The New England
Journal of Medicine

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Volume 233 NOVEMBER 8, 1945 Number 19

NONTUBERCULOUS PNEUMONIA COMPLICATING PULMONARY TUBERCULOSIS

A Review of One Hundred and Eleven Cases*

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FOR many years, certain clinicians have discussed the relation between pulmonary tuberculosis and pneumonia occurring in the same patient. Opinion has been unanimous concerning the low incidence of the combined diseases, but when explanations have been offered concerning the reasons for the low incidence, much diversity has appeared. There has been similar disagreement about the effect that either disease has on the other. In only a few cases have opinions been supported by case reports. This study was therefore undertaken in an attempt to answer the following questions: What is the incidence of these two diseases occurring in the same person? Are the course and outcome of the pneumonia altered by the presence of tuberculosis, whether active or inactive? Are the course and outcome of the tuberculosis altered by a superimposed pneumonia? Can any therapeutic inferences be drawn from this study?

REVIEW OF THE LITERATURE

Opinions in the literature concerning the relation between pneumonia and tuberculosis are few, and the reports of cases cited to substantiate such opinions are even fewer. Reports occurring prior to 1900 — mostly in the German literature — were vitiated by inability to exclude the ever-present possibility of the pneumonia's being tuberculous. This handicap was overcome with the advent and use of the x-ray and more exact bacteriologic data.

All agree that the incidence of the simultaneous presence of these diseases is significantly low. Baum and Amberson[1] quote Frankel as having observed 15 cases of pneumonia among 3250 tuberculous patients (0.46 per cent), and Schroder as having seen 2 cases in 6000 patients. Cecil[2] reports that pneumonia occurred in 2 patients out of 5000 at the Trudeau Sanatorium. Brock is quoted as having seen only 1 case of pneumonia and tuberculosis in thirteen years at Waverly Hills Sanatorium,[3] and Heise,[4] after thirty-five years of experience with sanatorium patients, has observed less than 6 such cases. Hayes[5] states that among the tuberculous true lobar pneumonia is rare.

Similarly, in large series of pneumonia patients tuberculosis is rarely found. Frankel noted 15 such cases in 760 cases of pneumonia.[6] Finland and his associates[7] noted 33 cases of tuberculosis among 684 autopsies of patients dying of pneumococcal pneumonia. He[8] further reports finding 29 patients with a positive sputum in a series of 3682 cases of pneumococcal pneumonia. Moore and his associates,[9] grouping together pulmonary tuberculosis, recurrent pleurisy and pneumoconiosis, found only 24 such cases among 1469 pneumonia patients.

Few investigators have attempted to explain this low incidence. Calmett and Saenz[10] found tuberculous guinea pigs especially resistant to inhalation infection with virulent pneumococci. Weissfeiler[11] explained this resistance on the basis of a nonspecific allergic reaction — the so-called "heteroallergic response." He was able to produce a typical Koch's phenomenon with organisms other than the tubercle bacillus, and by analogy he reasoned that likewise secondary invaders in a tuberculous patient set up a violent allergic response that destroys the invader before infection can be started.

Concerning the effect on the course and outcome of the pneumonia in this combination, there is a dearth of information. Bieling and Oelrichs[12] report that tuberculous rabbits react more vigorously to infection with pneumococci than do normal animals, but that the final outcome favors the tuberculous rabbits. Weissfeiler and others,[13] trying to determine whether the course of the pneumonia is altered in rabbits with far-advanced tuberculosis, injected Type 1 pneumococci intraperitoneally and intravenously. The reaction in the tuberculous rabbits was slower and more exudative in type and tended more toward necrosis than in

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normal animals, and in response to the added infection a proportionately larger role was played by the reticuloendothelial system. Finland and his co-workers[7] state that the pneumonia associated with tuberculosis is likely to be bronchopneumonic in character and to be caused by a pneumococcus of Type 3, 8, 10, 18 or 20. In another report, he[8] concludes that pneumococcal bronchopneumonia is usually a secondary complication of other serious disease, and hence has a higher mortality rate than do other types. Moore et al.[14] believe that tuberculosis lowers the resistance to pneumococcal infection and that its presence increases the complication rate.

The effect of intercurrent pulmonary infections on the tuberculous process has been studied somewhat more thoroughly. Thus during the pandemic of influenza in 1918–1919 several reports appeared in the literature showing that activation of the tuberculosis took place in as many as 50 per cent of some series.[15–17] Similarly, many authors have been concerned with the activation that occurs with lung abscesses and purulent lung infections.[18] When one comes to pneumonia, however, the only extensive investigation was conducted by Baum and Amberson.[1] They presented a series of 102 cases of pneumonia in 97 tuberculous patients. Because of the size of this group, they concluded that pneumonia was not rare in the tuberculous population, although they do not state the incidence that they observed. They believe that pneumonia has potentialities for causing activation of a tuberculous lesion, for in their series definite activation was caused in 8 cases, probable activation in 10 and doubtful activation in 11. Sixty-five cases showed no activation.

The attempt to explain the pathogenesis of reactivation brings forth several possibilities. Krause[19] believes that the inflammation with its attendant congestion puts such a strain on the fibrous capsule that surrounds the tuberculous nodule that this capsule is gradually destroyed, resulting in the liberation of the tubercle bacilli. Pagel[20] explains it on the basis of heteroallergy, and shows that liquefaction is a result of this allergic response — a response that can be set up by secondary invaders like the pneumococcus.

Perhaps the most important factor, however, is the destruction of the capsule by pulmonary suppuration. This point is well taken by Baum and Amberson,[1] who observed a high incidence of activation in cases of bronchiectasis and in lung abscesses. Destruction by aputrid necrosis likewise can set the bacilli free. Kessel[21] has adequately described this type of pulmonary parenchymal necrosis as occurring in areas of resolving pneumonia. He attributes the destruction to thrombosis of the artery supplying the area involved, with ensuing infarction and formation of an aputrid abscess. Because these areas frequently do not open to a bronchus, the abscess remains uncontaminated by pyogenic organisms. He holds that thromboses of tiny end arteries are frequent and that the small cavities produced, although not of sufficient size to give evidence of their presence, may easily result in autolysis of the fibrous tuberculous capsule. These areas of necrosis have been commented on by other authors as well.[22–24]

Baum and Amberson[1] conclude as follows:

> We believe that the reason for the failure of pneumonia to activate the majority of tuberculosis cases lies in the site of attack by the most frequent infecting organism — the pneumococcus. This organism is primarily an alveolar pathogen and interstitial invasion is the exception rather than the rule, conspicuous only in Type 3. . . . Suppuration within the pneumonic area is the most important factor in subsequent activation of a tuberculous lesion.

In regard to Type 3, all those who have dealt with large series of cases have recognized the unusual invasive features of Type 3 pneumonia.[7,8,25]

Poindexter[26] has furnished evidence that the presence of secondary organisms heightens the virulence of the tubercle bacillus. McPhedran,[27] at the other extreme, has presented a series of 51 cases of tuberculosis, one third of which were probably inactive, in each of which the development of a nonspecific parenchymal infection in one or both paracardiac areas was followed by regression of the tuberculous lesion in one of the upper lobes. In another communication, however, he[28] reports 4 cases, among others, in which a bronchopneumonia caused miliary spread of tuberculosis by "flooding" the nodes rather than by depressing resistance. He[29] maintains:

> The chief effect on pre-existent tuberculous lesions of acute pulmonary respiratory disease is probably a quasi-mechanical one, whereby the lymph drainage, increased by the acute infection, sweeps into the circulation tubercle bacilli from the already extensively damaged lymph node.

Five papers have been discovered in the English literature that present case reports. In 1937, Pagel[30] reported a case of pneumonia occurring in a patient with quiescent tuberculosis, and offered the first definite histologic proof of liquefaction and liberation of the tubercle bacilli by the pneumonic process. In 1939, Crawford[31] presented a case of fibrocaseous and cavernous tuberculosis in the right upper lobe and right midzone, with mottling in the entire left lung and a cavity in the left upper lobe. A pneumonic consolidation occurred in the right lower lobe, and the sputum was found to contain both Type 1 pneumococcus and tubercle bacilli. The patient developed a Type 1 empyema, was treated with sulfanilamide and recovered with no increase in the tuberculosis. In 1940, Moolten,[24] reporting a case of pancreatic lithiasis, called attention to the findings of a pneumonia in the right upper lobe previously involved in a tuberculous process. He described the histologic picture of destruction of the envelope of scar tissue around the tubercles, with release of caseous contents, and the adjacent

secondary patches of recent active tuberculosis. He concluded that the pneumonia reactivated the tuberculosis by a necrotizing process. In 1941, Pedigo and Coleman[3] reported a sanatorium patient with active tuberculosis who was treated with sulfonamides, with recovery from the pneumonia and no increase in the tuberculosis, and an ex-sanatorium patient with questionably active tuberculosis who was similarly treated with sulfonamides, with recovery and with doubtful activation, a cavity having been noted six weeks after the onset of pneumonia. A third patient was found at autopsy to have Type 3 pneumonia and a fibrocalcific tuberculous lesion in the same lobe, the latter showing no evidence of reactivation.

Finally, in 1942 was published the classic article of Baum and Amberson,[1] to which frequent reference has already been made. Appended to their paper is an extensive bibliography that covers many phases of nontuberculous pulmonary infections complicating pulmonary tuberculosis, not included within the scope of this paper.

Analysis of Cases

This section is concerned with a review of 111 cases of pneumonia complicating tuberculosis in 104 patients; 5 patients had more than one attack. These 111 cases constitute all the proved cases in which the patients were discharged from the Philadelphia General Hospital with the combined diagnoses, all of them between June, 1936, and June, 1944. Patients in whom one of the diseases was merely suspected were excluded from the study, as were all cases of tuberculous pneumonia. None of the patients were observed personally, all the data here presented having been assembled from the hospital records.

Almost all the roentgenograms were interpreted by one or the other of the two senior members of the Radiology Department, and the remainder by the resident radiologist. All the laboratory work was performed in the hospital laboratories by experienced personnel.

In this series there were 42 deaths, a mortality rate of 40 per cent, based on the number of patients. Autopsies were performed in 35 cases.

Pneumonia

The diagnosis of pneumonia was made on the basis of the history, physical findings and x-ray reports and the discovery of pneumococci in the blood or sputum. In the history, emphasis was placed on onset with chills, fever, pain on respiration, cough, a rusty sputum and dyspnea. Greater attention was paid to rigor and rusty sputum because of their rarity in tuberculous pneumonia and their frequent presence in pneumococcal lobar pneumonia. In addition to the finding on examination of evidence of infiltration or consolidation in the lungs, special attention was paid to the presence of herpes labialis, which likewise has been found to be most unusual in tuberculous pneumonia.

In classifying the cases of pneumonia it was found that the terms "lobar pneumonia" and "bronchopneumonia" were insufficient because of their lack of specificity. To be sure, in discussing the relation between tuberculosis and pneumonia it is requisite to be as certain of the etiology of the pneumonia as of that of the tuberculosis. Hence, the pneumonia cases were divided into the following three groups in an effort to combine specificity with the x-ray and clinical classifications: Group 1 (45 cases), pneumococcal lobar pneumonia; Group 2 (23 cases), pneumococcal bronchopneumonia; and Group 3 (43 cases), bronchopneumonia of undetermined etiology.

In Group 1 there were 6 patients who had no adequate bacteriologic studies, but they are included because of the otherwise typical history, physical findings, x-ray appearances, response to treatment, typical resolution and so forth. In 3 of these patients, autopsy confirmed the diagnosis. The possibility of staphylococcal or streptococcal lobar pneumonia is recognized, but little significance can be attached to the erroneous inclusion of the rare case.

Group 3 in all probability contains many cases that would have been put in Group 2 if bacteriologic studies had been made, for in only 2 cases was this done, with a positive report for another organism (*Streptococcus haemolyticus*).

Table 1 summarizes the historical features of the complete series considered solely from the standpoint of the pneumonia. Attention is directed to the fact that the time between the onset of symptoms and admission to the hospital was much longer in Group 3 than in the two other groups, and to the symptoms in all groups, which in order of frequency were cough, fever, pain, dyspnea, chills, a rusty sputum and herpes labialis. The last occurred only in the cases of pneumococcal pneumonia. Great discrepancy is likewise noted between the incidence of chills in Group 1 as compared with Groups 2 and 3.

In regard to the number of symptoms per patient, pneumonia was considered the likeliest diagnosis on the basis of the history alone if four or more symptoms were present. This was so in 51 per cent of the patients in all these groups.

Table 2 summarizes some of the physical findings, including involvement as determined by physical and x-ray examination.

Table 3 summarizes the important laboratory data, and Table 4 the treatment directed toward the pneumonia and the outcome. The high percentage of deaths in the total series (38 per cent) is due to the moribund condition of some patients on admission, as well as to the occurrence of pneumonia before the advent of the sulfonamides.

Tuberculosis

Tuberculosis was known to have existed in 40 of the 111 cases. Thirty-four of these patients had been under treatment at a hospital at one time or another, and 6 were under treatment at the time of the development of pneumonia. There were in addition 14 patients with a decidedly typical history and repeated close contact with open tuberculosis at home, who were consequently considered to have the disease on admission. Hence, there were 54 patients in whom tuberculosis was, with relative certainty, known to be present at the onset of pneumonia. In the remaining 57 cases, the tuberculosis was diagnosed after admission, mainly on the basis of x-ray evidence or the presence of tubercle bacilli in the sputum. In fact, most of the patients came to the hospital because of the pneumonia. Only 35 were either admitted to the tuberculosis wards or were already on those wards when pneumonia developed. The rest were sent to the Fever Ward — a special ward for pneumonia patients.

The tuberculosis was classified as active (32 cases) and inactive (79 cases) (Table 5). The disease was considered to be active if it was known to have been so shortly before the onset of the pneumonia, or if there was a positive sputum or x-ray evidence of cavitation or soft, exudative lesions that showed marked changes from one film to the next. Otherwise it was considered to be inactive.

TABLE 1. *Historical Features of 111 Cases of Simultaneous Pneumonia and Tuberculosis, Considered from the Standpoint of the Pneumonia.*

Historical Feature	Pneumococcal Lobar Pneumonia	Pneumococcal Broncho-pneumonia	Broncho-pneumonia of Undetermined Etiology	Totals
Age:				
0-9 yr.	0	1	1	2
10-19 yr.	0	1	3	4
20-29 yr.	4	0	1	5
30-39 yr.	11	3	5	19
40-49 yr.	11	6	5	22
50-59 yr.	11	5	10	26
60-69 yr.	6	2	13	21
70 yr.	2	5	5	12
Sex:				
Male	30	18	29	77
Female	15	5	14	34
Color:				
White	28	17	31	76
Negro	17	6	12	35
Time from onset to admission:				
1 day	4	5	4	13
2 days	3	0	1	4
3 days	5	3	2	10
4 days	7	2	3	12
5 days	5	0	2	7
6 days	6	4	1	11
7 days	2	3	4	9
8 days	1	1	1	3
9 days	2	0	0	2
10 days	5	1	1	7
11 days	2	4	13	19
Unknown	3	0	11	14
Major symptoms:				
Cough	42 (96%)	22 (95%)	40 (93%)	104 (94%)
Fever	44 (98%)	22 (95%)	35 (81%)	101 (90%)
Pain	32 (72%)	16 (70%)	20 (46%)	68 (61%)
Dyspn.	31 (70%)	8 (35%)	26 (60%)	65 (59%)
Chills	29 (64%)	9 (39%)	13 (30%)	51 (46%)
R. sput.	16 (36%)	7 (30%)	6 (14%)	29 (26%)
Herpes	5 (11%)	1 (4%)	0	6 (5%)
Number of symptoms per patient:				
1	0	0	2	2
2	4	4	10	18
3	6	8	10	24
4	12	5	16	33
5	13 (78%)	3 (48%)	5 (49%)	21 (51%)
6 or 7	10	3	0	13

TABLE 2. *Case Incidence of Clinical and Roentgenographic Findings.*

Finding	Pneumococcal Lobar Pneumonia	Pneumococcal Broncho-pneumonia	Broncho-pneumonia of Undetermined Etiology	Totals
Temperature on admission:				
99 or lower	3	2	13	18
100	4	3	7	14
101	6	4	8	18
102	12	8	8	28
103	7	4	4	15
104 or higher	13	2	3	18
Number of lobes involved:				
1	28	13	23	64
2	15	7	10	32
3 or more	2	3	10	15
Frequency of significant disease other than tuberculosis:	26	9	19	54 (50%)

TABLE 3. *Case Incidence of Significant Important Laboratory Findings.*

	Pneumococcal Lobar Pneumonia	Pneumococcal Broncho-pneumonia	Broncho-pneumonia of Undetermined Etiology	Totals
Maximum white-cell count (in thousands):				
5-9	2	4	4	10
10-14	6	4	2	12
15-19	10	3	3	16
20-24	6	4	1	11
25-29	8	2	2	12
30 or over	7	1	2	10
Percentage of neutrophils in total white-cell count:				
40-49	1	0	0	1
50-59	0	1	0	1
60-69	0	0	1	1
70-79	4	2	5	11
80-89	13	12	4	29
90-100	21	4	4	29
Blood culture:				
Positive	10	1	0	11
Negative	23	7	4	34
Organisms in sputum or blood, or both:				
Pneumococcus:				
Type 1	4	1	—	5
Type 2	2	1	—	3
Type 3	4	0	—	4
Type 4	4	1	—	5
Type 5	1	2	—	3
Type 6	1	1	—	2
Type 7	3	0	—	3
Type 8	3	0	—	3
Type 13	0	1	—	1
Type 16	1	0	—	1
Type 17	1	0	—	1
Type 20	2	1	—	3
Type 22	1	0	—	1
Type 25	1	0	—	1
Untyped	8	15	—	23
Secondary to pneumococcus	10	8	—	18
Other than pneumococcus	2		2	4
Not examined	7		41	48

TABLE 4. *Treatment Directed toward Pneumonia, and Outcome.*

Type of Treatment	Pneumococcal Lobar Pneumonia		Pneumococcal Broncho-pneumonia		Broncho-pneumonia of Undetermined Etiology		Totals	
	Living	Dead	Living	Dead	Living	Dead	Living	Dead
Sulfonamides	20	8	10	2	8	2	38	12
Antipneumococcus serum	1	0	0	0	0	0	1	0
Sulfonamides and serum	4	2	1	0	0	0	5	2
Supportive treatment	8	1	6	4	11	16	25	21
No treatment	0	1	0	0	0	6	0	7
Totals	33	12	17	6	19	24	69	42

Treatment of the tuberculosis, when it was discovered, was given according to the usual procedure followed in the Division of Tuberculosis — bed rest with supplementary treatment when indicated.

Pneumonia and Tuberculosis Combined

The foregoing sections have analyzed this series as composed of some patients with pneumonia of one sort or another, and of others with pulmonary tuberculosis in some stage of activity or healing. The series will now be considered from the viewpoint of the two diseases combined. The incidence of the combination, as in the reports of other investigators, was low. During the period covered by this study, there were 6737 cases diagnosed as pneumonia, the incidence of tuberculosis among which was 1.6 per cent. During the same period there were 8487 patients with tuberculosis. Hence, the incidence of pneumonia among the tuberculous patients was 1.3 per cent, and the incidence of the combination among the total patients with tuberculosis or pneumonia was 0.73 per cent. Regardless of how one calculates the incidence, the fact that these two extremely prevalent diseases occur in combination in such a low incidence is startling. Obviously this requires explanation. Some opinions on this question were quoted above in the review of the literature; further brief comment on this point will be made in the discussion.

Table 5. *Activity of Tuberculosis in the Pneumonia Groups.*

	Pneumococcal Lobar Pneumonia	Pneumococcal Broncho-pneumonia	Broncho-pneumonia of Undetermined Etiology	Totals
Active	16	2	14	32 (29%)
Inactive	29	21	29	79 (71%)
Totals	45	23	43	111

The next question is the effect that tuberculosis has on the course and outcome of pneumonia. When this series is compared with large series of uncomplicated cases of pneumonia, it is seen that the onset and clinical manifestations approximate closely, but this is not true as concerns the course and outcome.

Course

The cases have been grouped as those with a typical course and those with an atypical one. The course was considered typical if there was crisis or lysis of the fever, clinical improvement and recovery and no sequelae, such as empyema, recurrent fever and so forth. The reverse of these criteria constituted an atypical course, and these patients naturally included all those who died during the pneumonia. Since 60 of these patients were treated specifically (Table 4), it is desirable to know whether the course was altered in the treated group as compared with the untreated group in relation to the degree of activity of the tuberculosis. Table 6 summarizes the data on this point.

It will be seen that the course of the pneumonia was atypical in 23 (72 per cent) of the 32 cases with active tuberculosis and in 43 (54 per cent) of the 79 cases with healed or inactive tuberculosis. There are so many other variables that it is impossible to ascribe this difference solely to the presence of tuberculosis in active form, but it seems reasonable to conclude that the course of the pneumonia is likelier to be altered if the tuberculosis is active than if it is healed or quiescent.

Again, of the 14 active cases that received specific treatment 10 (71 per cent) ran an atypical course, whereas of the 18 that received no specific treatment 13 (72 per cent) did so. Of the 48 inactive cases that received specific therapy 23 (48 per cent) ran an atypical course, and of the 29 that received no specific treatment 20 (69 per cent) did so. Hence, it seems that the number of tuberculous patients with pneumonia who run an atypical course is not altered to any great degree by the specific therapy of the pneumonia, except in those with inactive tuberculosis. This is not to say, however, that the sulfonamides did not modify the clinical course of pneumonia in certain cases. Furthermore, this is perhaps an unfair judgment of the efficacy of the sulfonamides, since in many of the patients death probably occurred before adequate blood levels of the drug had been obtained.

Table 6. *Course of Pneumonia in Relation to Specific Treatment and Activity of Tuberculosis.*

Type of Tuberculosis	Pneumococcal Lobar Pneumonia				Pneumococcal Broncho-pneumonia				Bronchopneumonia of Undetermined Etiology				Totals
	Typical		Atypical		Typical		Atypical		Typical		Atypical		
	Specific Treatment	Non-specific Treatment	Specific Treatment	Non-specific Treatment	Specific Treatment	Non-specific Treatment	Specific Treatment	Non-specific Treatment	Specific Treatment	Non-specific Treatment	Specific Treatment	Non-specific Treatment	
Active	4	0	9	3	0	1	0	1	0	4	1	9	32 (29%)
Inactive	11	3	12	3	6	4	9	2	8	4	2	15	79 (71%)
Totals	15	3	21	6	6	5	9	3	8	8	3	24	111

Outcome

The effect of tuberculosis on the outcome of pneumonia is shown in Table 7. Among the 32 active cases, death occurred in 18 (56 per cent), and among the 79 inactive cases it occurred in 24 (30 per cent). Thus, the deaths were twice as numerous when the tuberculosis was active than when it was inactive.

It is now to be determined whether tuberculosis is altered by superimposed pneumonia. To this end, the series has been regrouped according to whether the tuberculosis was activated and to what degree — that is, definite activation, probable activation, doubtful activation, no activation and activation unknown. In so doing, the criteria of Baum and Amberson have been employed. They state:

> Definite activation was thought to have taken place when there was post-mortem evidence of recent activation or when, following pneumonia, pulmonary tuberculosis, which previously had been stationary or latent, became progressive.
>
> To the category of probable activation were assigned cases in which previously inactive pulmonary tuberculosis showed signs of activity, though not of progression; there was spread of previously active tuberculosis coinciding with the pneumonia; and early death was due apparently to progressive tuberculosis, although post-mortem examination was lacking.
>
> The category of doubtful activation included cases of tuberculosis showing temporarily a positive sputum during the course of pneumonia; cases showing residual areas of density in the roentgenogram, in which differentiation between spread of tuberculosis and postpneumonic pulmonary fibrosis was not possible; and cases showing progression of tuberculosis later than one month but sooner than one year after subsidence of the pneumonia.
>
> No activation was considered to have taken place when there was no change in the tuberculous lesion or its activity, or when progression of the tuberculosis occurred later than one year after subsidence of pneumonia, the latter having left behind no suppurative lung disease.
>
> The degree of activation was considered to be unknown when death occurred too soon to show an effect clinically and when no post-mortem examination was done. It was also considered unknown when no adequate information was at hand regarding the status of tuberculosis at the time the pneumonia took place, even though there was progressive tuberculosis following the pneumonia.

Table 8 shows the number of cases in each category in relation to the pneumonia. The rather large number of patients in the doubtful group were placed there mainly because of residual shadows that persisted four or more weeks after the onset of pneumonia. Since more and more cases of slowly resolving pneumonia are coming into the reported series, it is quite probable that some of these, especially those in Group 3, were virus or other slowly resolving types of pneumonia, and that if more accurate diagnostic facilities had been available they would have been grouped with those that showed no reactivation.

TABLE 7. *Outcome of Pneumonia in Relation to Type of Therapy and Activity of Tuberculosis.*

Type of Tuberculosis	Pneumococcal Lobar Pneumonia		Pneumococcal Bronchopneumonia		Bronchopneumonia of Undetermined Etiology		Totals
	specific treatment	nonspecific treatment	specific treatment	nonspecific treatment	specific treatment	nonspecific treatment	
Active:							
Alive	6	3	0	1	0	4	14
Dead	6	1	0	1	1	9	18
Inactive:							
Alive	18	6	11	5	8	7	55
Dead	4	1	2	3	1	13	24
Totals	34	11	13	10	10	33	111

TABLE 8. *Type of Activation according to Type of Pneumonia.*

Type of Activation	Pneumococcal Lobar Pneumonia	Pneumococcal Bronchopneumonia	Bronchopneumonia of Undetermined Etiology	Totals
Definite	2	1	0	3
Probable	1	0	0	1
Doubtful	5	5	5	15
None	28	14	34	76 (68%)
Unknown	9	3	4	16
Totals	45	23	43	111

In the unknown group, several showed progressive disease, but they were so placed because the prepneumonic status of the tuberculosis could not be determined. It was similarly probable that some of these rightfully belong in the group with definite activation.

Table 9 shows the occurrence of reactivation in relation to the type of tissue reaction of the tuberculosis. It is considered that definite, probable or even doubtful reactivation is a serious alteration of the disease. Furthermore, in most cases this reactivation, despite other variables, was probably due to superimposed pneumonia.

TABLE 9. *Reactivation of Different Pathologic Types of Tuberculosis.*

Type of Tissue Disease	Type of Reactivation					Totals
	definite	probable	doubtful	none	unknown	
Predominately exudative	1	0	2	5	4	12
Predominately fibroproductive	0	0	8	25	5	38
Fibrocavernous	1	1	1	12	4	19
Fibroid and calcific	1	0	4	32	3	40
Under collapse therapy	0	0	0	2	0	2
Totals	3	1	15	76	16	111

Table 10 shows the topographic relation of pneumonia and tuberculosis. In 46 cases in the series (41 per cent), at least one lobe was involved by both diseases. Each case was counted once even though more than one lobe was involved in either process. The remaining 59 per cent had pneumonia in a lobe or lobes that were not involved by tuberculosis. It is seen that 83 per cent of the total fall into the group of doubtful or no activation. This permits the conclusion that superimposed tuberculosis is likely to give rise to reactivation of tuberculosis in approximately 15 per cent of cases.

Discussion

The preceding section has given a statistical analysis of these cases. To obtain a clearer picture of the situation, certain points need comment. Thus, the extremely low incidence of the combination of pneumonia and tuberculosis has been noted. The fact that these diseases occur together is beyond dispute. One should note, however, that the tuberculosis was active in only 29 per cent of the series, and that in little less than half of these the pneumonia was a terminal event. Hence, one rarely finds a tuberculous patient with active disease who develops pneumonia and recovers from it and continues to have active tuberculosis. According to the records of the Philadelphia General Hospital, with 2700 beds, it occurred in only 14 cases in eight years. Baum and Amberson[1] are inclined to attribute this extraordinarily low incidence in part to the sheltered life of sanatorium patients, but this institution is a city hospital with chiefly charity beds, and its patients in the main lead quite the reverse of sheltered lives.

Table 10. *Topographical Relation between Pneumonia and Tuberculosis.*

Location of Pneumonia	Reactivation of Tuberculosis: definite or probable	doubtful or none	unknown	Totals
Pneumonia in tuberculous lobe	3	38	5	46 (41%)
Pneumonia not in tuberculous lobe	1	54	10	65 (59%)
Totals	4	92	15	111

Is there some antithesis between the growth characteristics of the pneumococcus and those of the tubercle bacillus such as to prevent their simultaneous growth? This is a question to which there is at present no adequate answer. The views of others, quoted above, present explanations that are not completely satisfactory.

Conclusions

From this study the following conclusions may be drawn. First, the incidence of pneumonia complicating pulmonary tuberculosis is significantly low. The occurrence of nonterminal pneumonia in a patient with active tuberculosis is extremely infrequent, less than 2 cases a year being observed at the Philadelphia General Hospital. Second, the course of pneumonia is altered by the presence of tuberculosis. Of this series of 111 cases, 60 per cent ran an atypical course — 72 per cent of the active cases and 54 per cent of the inactive ones. Third, the outcome of pneumonia is altered by the presence of tuberculosis. In this series the death rate was 38 per cent, but the deaths were almost twice as numerous when the tuberculosis was active (56 per cent) as when it was inactive (30 per cent). Fourth, reactivation of a tuberculous focus that is quiescent or an increase of disease in already active tuberculosis may be expected in 15 per cent of the patients who develop superimposed pneumonia, whether or not it is in the same lobe and whether or not it is specifically treated. Lastly, no definite therapeutic implications have been derived from this study. The question of bacterial antagonism was not a subject of this paper, but if this is the correct explanation of the infrequency of pneumonia complicating tuberculosis, therapeutic use of the products of the pneumococcus might well be made in the treatment of pulmonary tuberculosis. This appears to be a fertile field for future investigation.

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Case Reports

Case 1 (No. 127446). The patient, a 56-year-old Negress, was apparently in usual health until 2 weeks before admission, when she developed a "cold." Not long afterward she had chills and fever, became short of breath and noted pain in the right lower chest, aggravated by inspiration and coughing. These symptoms were severe during the 3 days prior to admission. There was no hemoptysis and no history of previous respiratory disease.

On admission the patient was acutely ill, mildly confused and markedly dyspneic. The temperature was 103°F., the pulse 120, and the respirations 60. Coarse rales were heard throughout the lung fields, but there was definite evidence of consolidation of the right lower lobe. Treatment was started with sulfamerazine, but because of the patient's serious condition she was placed in an oxygen tent. Despite all efforts she died within 12 hours of admission.

Autopsy disclosed a typical lobar pneumonia of the right lower lobe, bronchopneumonia of the left lower lobe and fibroexudative tuberculosis of the left upper lobe, with recent tuberculosis of the right upper lobe. Histologically the pneumonia was shown to be nontuberculous.

Comment. This patient was found to have active tuberculosis with active pulmonary inflammation, probably pneumococcal in origin. The fact that she was apparently well until approximately 2 weeks before admission indicates that the tuberculosis found in the right upper lobe was a recent spread from a newly activated focus in what was probably an area of quiescent tuberculosis, the reactivation occurring in the course of the secondary infection of the lung. It is of interest that the lobe that was consolidated was not the one that harbored the original tuberculous infection. This case is classified as one of definite reactivation.

Case 2 (No. 94071). The patient, a 68-year-old Negro, was admitted in a feeble condition. The history was incomplete, but he had been sick for 4 weeks with a nonproductive cough, weight loss, night sweats and indefinite chest pain.

On admission, the temperature was 101°F. There was jaundice, and evidence of consolidation was found over the left upper and right middle lobes. A diagnosis of bilateral pulmonary tuberculosis was made. A throat culture grew pneumococci, and a blood culture made on admission grew Type 8 pneumococci. The icteric index was 48. X-ray examination of the chest showed consolidation of the right upper and middle lobes and the left upper lobe.

The patient was treated with sulfadiazine, with only a fair response. Six days after admission, he developed consolidation of the left lower lobe. A repeat blood culture was negative. He grew weaker and died.

Autopsy showed pneumococcal lobar pneumonia involving the right upper and the left lower lobes, with marked organization, together with bilateral chronic apical tuberculous cavitation. The patient was also suffering from lymphoid leukemia, which was discovered in the histologic sections.

Comment. This patient had a proved active lobar pneumococcal pneumonia with pneumococcemia and simultaneously active cavernous tuberculosis. One of the tuberculous lobes was also involved in the process of lobar consolidation. Yet no evidence of reactivation was demonstrable, and death was ascribed to the pneumonia.

Case 3 (No. 89869). The patient, a 41-year-old Negress, was admitted in a critical condition. For several months she had had a chronic cough and night sweats, together with weight loss, but no hemoptysis. Fourteen days before admission she "caught cold." Ten days before admission she had a chill and developed a fever and cough, with brownish sputum. She received sulfapyridine before coming to the hospital, to no avail.

On admission the patient was extremely ill; the temperature was 102°F., the pulse 120, and the respirations 30. There was consolidation of the entire right lung. A diagnosis of tuberculosis and pneumonia was made. Treatment was started with sulfathiazole. A culture of the sputum revealed Type 25 pneumococcus, and a 24-hour concentrate was negative for tubercle bacilli. The white-cell count was 26,100, with 79 per cent polymorphonuclear leukocytes and 18 per cent lymphocytes. X-ray examination revealed consolidation of the entire right lung.

Despite treatment during the next 18 days, the patient ran a continual fever that spiked between 99 and 102°F. She then became suddenly worse, developed signs of meningitis and was found to have a Type 25 pneumococcemia and pneumococcal meningitis. She died 2 days later.

Post-mortem examination showed in addition to purulent meningitis a chronic cavernous tuberculosis in the right upper lobe and unresolved pneumococcal pneumonia in the right lower lobe.

Comment. In this case also, although both conditions occurred in an active phase, no evidence of activation or increase in the tuberculosis was demonstrated.

Case 4 (No. 122759). The patient, a 58-year-old man, was well and working until 6 days before admission, when he had a severe chill followed by fever. He soon developed a cough productive of blood-streaked sputum, severe pain in the right upper chest, aggravated by deep inspiration and coughing, and shortness of breath. He had been in good health until the onset of the present illness. There were no prior symptoms referable to the respiratory tract.

Examination on admission showed the patient to be acutely ill. The temperature was 102°F., the pulse 128 and the respirations 68. There was consolidation of the right upper and middle lobes and infiltration in the left upper lobe, and auricular fibrillation. Cultures of the sputum and blood disclosed Type 1 pneumococcus in each. The white-cell count was 33,800, with 88 per cent polymorphonuclear leukocytes. An electrocardiogram confirmed the auricular fibrillation.

The patient was treated with digitalis and sulfadiazine and placed in an oxygen tent. The temperature dropped to normal within 2 days, and remained normal for 3 days, when it began to show a daily afternoon rise. Seven days after admission, the patient was much improved and required no supplementary oxygen, but the consolidation remained over the right upper lobe and anorexia, weakness and productive cough continued. On the 14th day, an electrocardiogram revealed that the auricular fibrillation had given way to a normal rhythm. A chest film showed dense infiltration of both upper lobes, with cavities in both. Three sputum specimens were negative for tubercle bacilli, but a fourth, taken 3 weeks after admission, was positive. The patient was then treated for active tuberculosis. Approximately 1 year after admission and after a left 7-rib thoracoplasty, he was discharged to a sanatorium for continued convalescence.

Comment. This case is one in which tuberculosis must have been present and active although the patient was asymptomatic. A definite lobar consolidation with bacteremia occurred in the area of tuberculous infection. Because the patient was symptomless before the pneumonia and had symptoms following it, there was probably definite increase in the tuberculosis, but because the exact status of the tuberculous infection prior to the pneumonia is not known, the case is included in the category of probable reactivation.

Case 5 (No. 103042). The patient, a 31-year-old Negress, had been well until 2 weeks prior to admission, when she developed a cough with expectoration, fever and malaise, all of which grew worse until admission. She was subject to "colds," during which she often expectorated blood.

On admission the patient was extremely ill. The temperature was 103°F., the pulse 135, and the respirations 35. There was moderate dyspnea and signs of consolidation of the entire left lung. Sputum and blood cultures both disclosed Type 16 pneumococcus. The white-cell count was 24,600, with 80 per cent polymorphonuclear leukocytes.

Treatment was supportive and consisted of massive doses of Type 16 antiserum. Daily blood cultures remained positive for Type 16 pneumococcus for the next 5 days. The temperature fluctuated between 99 and 103°F. for 6 days, when the patient began to run a low-grade fever ranging between normal and 101°F. Because of persistent chest signs, an x-ray film was taken 3 weeks after admission; this revealed soft mottling throughout

the left lung, with several small cavities in the 1st and 2nd interspaces. Twelve days later, another chest film disclosed some increase of disease in the left lung, with cavitation present in both the left upper and left lower lobes. After the first x-ray report sputum studies were undertaken, but a positive sputum was not obtained until 6 months after admission. Subsequently, the patient went downhill, the disease spread to the opposite lung, and she died of widespread tuberculosis.

Comment. Because of her history of frequent colds with expectoration of blood, it may be assumed that this patient had active pulmonary tuberculosis. A multilobar invasion with the pneumococcus resulted, in all probability, in the rapid spread of the tuberculosis in the lobes that were involved in the superimposed inflammation. Although this is probably one of the most definite cases of active tuberculosis with superimposed lobar pneumonia yet encountered, because of the lack of knowledge of the status of the tuberculosis at onset it is classified as probable reactivation. It is of interest that this patient was one of the 9 who had active tuberculosis with a superimposed pneumococcal lobar pneumonia but did not die during the pneumonia — that is, from the combination of the two diseases.

Case 6 (No. 74913). The patient, a 29-year-old man, was admitted with a history of known pulmonary tuberculosis for 13 years, many of which were spent at a sanatorium. He was at home awaiting a call to return to the hospital for a left thoracoplasty for upper lobe disease. Two weeks before admission he had a sudden onset of chills, fever, pain around the left lower chest, increased by deep inspiration, and an increase in coughing and expectoration.

Physical signs on admission were those of atelectasis of the left upper lobe and consolidation of the left lower lobe. These findings were confirmed by x-ray examination, which in addition demonstrated healed disease in the right upper and middle lobes. A Type 17 pneumococcus was abundant in the sputum.

The course during the first week or so was stormy, with extreme dyspnea, cyanosis and a temperature that fluctuated between 100 and 102°F. On the 7th day, the administration of sulfathiazole was begun, and the patient gradually improved. Two weeks after admission, when he was clinically improved, the sputum was found to be positive for tubercle bacilli.

Three weeks after admission there was a relapse, with dyspnea, cyanosis and a temperature of 103°F. X-ray examination disclosed atelectasis of the left upper lobe and effusion at the left base. The chest was tapped, with removal of purulent fluid, culture of which revealed pneumococci but no tubercle bacilli. At that time the sputum still showed abundant Type 17 pneumococci. The patient received a course of sulfapyridine and within a few days seemed to be convalescing normally. Two weeks later he had a second relapse, with dyspnea, cyanosis and fever. Fluoroscopy demonstrated atelectasis of the left upper lobe, mottled density of the left lower lobe and scattered densities in the right lung. The next day the patient was found dead in bed.

Post-mortem examination showed fibrosis, atelectasis and encapsulated caseous tuberculosis with activation in the left lung, and nontuberculous bronchopneumonia in the right lung.

Comment. This case was one of long-standing pulmonary tuberculosis, which had become sufficiently stationary for a thoracoplasty to be planned. It appears that the lobar pneumonia was the starting point of the downward course. The case is unusual in that the patient not only developed lobar pneumonia but had a relapse with pneumococcal empyema and then a terminal bronchopneumonia, presumably due to the same organism. In view of the autopsy findings this case is classified as one of definite reactivation.

Case 7 (No. 56302). The patient, a 30-year-old woman, was known to have had tuberculosis for 12 years. The main lesions were in the right upper lobe. Five months prior to admission, checkup films revealed progression of the lesions. On the day before admission the patient developed a sudden pain in the left chest, fever, shortness of breath and an increase in cough and slight hemoptysis.

On admission, the temperature was 104°F., the pulse 150, and the respirations 50. Rales were heard throughout the chest, but there was evidence of consolidation of the left lower lobe. The patient was acutely ill and was placed in an oxygen tent and treated with sulfathiazole. The white-cell count was 10,600, with 92 per cent polymorphonuclear leukocytes. The sputum contained Type 2 pneumococci, but no tubercle bacilli were found. The course in the hospital was extremely hectic, and despite treatment death occurred 3 days after admission.

Autopsy disclosed typical lobar pneumonia in the left lower lobe, and caseous tuberculosis with cavitation in the right upper lobe.

Comment. This case was one of lobar pneumonia developing in a patient with active progressing tuberculosis, confirmed by autopsy. The cause of death was attributed equally to the pneumonia and to the tuberculosis. There was no reason to believe that the pneumonia caused any increase in the activity of the tuberculosis, especially since the patient did not live long enough to show whatever increase may have taken place. Hence, this case is placed in the no-reactivation group.

Case 8 (No. 123077). The patient, a 52-year-old man, entered the hospital with a 4-day history of acute illness. He had been working and well, except for a chronic cough, when he suddenly developed a chill, fever, chest pain and an increase in the cough, with production of thick, nonbloody sputum.

On admission, the temperature was 102°F., the pulse 118, and the respirations 28. There was evidence of scattered patches of consolidation in both lower lobes.

Treatment with sulfathiazole was begun, and within 2 days the temperature was normal, remaining so. The lung fields began to clear. An x-ray film taken on the 7th hospital day — 11 days after the onset — showed fibrous strands and pleural thickening in each apex, due to minimal healed tuberculosis, and haziness in the right base, due to recent pneumonia. The sputum was negative for tubercle bacilli. The patient had an uneventful convalescence and was discharged well after being hospitalized for 14 days. He remained well, although with some continued weight loss, for 6 months, at which time the cough and expectoration of greenish sputum increased. Three months later he was readmitted for these complaints. At this time he was found to have a positive sputum, and x-ray examination showed mottling and fibrosis of the entire right upper lobe, several small cavities in the 2nd interspace and bronchogenic spread to the midportion of the left lung. The patient continued to regress and died of widespread tuberculosis 5 months after the second admission.

Comment. This is a case of pneumonia developing in a person with apparently healed tuberculosis. Because the tuberculosis became reactivated between 6 and 9 months after the episode of pneumonia, the case is considered one of doubtful reactivation. Presumably, the lesion in the right upper lobe broke down and started the final illness. It is interesting to observe that the pneumonia was in the lower lobes and the tuberculosis in the upper, a fact that casts a little further doubt on the role of the pneumonia in the pathogenesis of reactivation.

Case 9 (No. 143818). The patient, a 38-year-old Negro, was well until 6 days before admission, when he developed a "cold." Soon afterward he had a chill, followed by chest pain, fever and cough productive of blood-tinged sputum.

On examination the temperature was 100°F., the pulse 120, and the respirations 35. There was evidence of consolidation of the right upper and middle lobes. Admission cultures of the throat and sputum were replete with pneumococci, but a blood culture was negative. The white-cell count was 19,400, with 84 per cent polymorphonuclear leukocytes. The patient was treated with sulfamerazine, and within 36 hours the temperature returned to normal, remaining so. On the 4th hospital day, x-ray examination revealed consolidation of the right upper and middle lobes. On the 7th day, a smear of the sputum was found to be positive for tubercle bacilli and the patient was transferred to the Tuberculosis Division. Subsequent to this there were positive sputums on the 30th, 38th and 50th days. Between these dates there were six negative sputums.

An x-ray film taken on the 20th day showed marked clearing of the consolidation in the right upper lobe and complete clearing in the middle lobe. A repeat film on the 35th day disclosed further clearing in the right upper lobe, so that there remained only a mild hazy infiltration at the right apex, which still had the appearance of a resolving pneumonia. The patient refused to stay in the hospital, and the final outcome of this lesion was never learned.

Comment. In this case lobar pneumonia occurred in a lobe that probably contained healed tuberculous lesions. The acute inflammatory process set free some of these organisms from time to time, and they were found in the sputum. For this reason, and because residual shadows persisted for more than 3 weeks, this case is classified as one of doubtful reactivation. It is possible that the healing of the pneumonic process was impaired because the reparative powers of the lung had previously been damaged by the healed tuberculous process.

CASE 10 (No. 130549). The patient, a 32-year-old man, was well until 2 weeks before admission, when he developed a "cold" with a nonproductive cough. One week before admission he experienced chills and fever and pain of a pleuritic type in the right lower anterior chest. A few days prior to entry, the cough became productive of nonbloody sputum. There was no personal or family history of tuberculosis.

On examination the temperature was 104°F., the pulse 108, and the respirations 30. Infiltration was discovered in both upper lobes. The white-cell count was 19,700 with 80 per cent polymorphonuclear leukocytes. Culture of the sputum disclosed pneumococci in abundance, and a smear for tubercle bacilli as well as a blood culture was negative.

The patient was treated with full doses of sulfamerazine. Although the temperature fell to 99°F. within 2 days, it began to spike to 101°F. daily for the next 6 days; it then returned to normal. Because of this atypical response of the temperature and because signs persisted in the left upper lobe, an x-ray film was taken 1 week after admission. It showed consolidation in the right upper lobe, and pleural thickening and fibrosis with a cavity beneath the clavicle in the left upper lobe. Soon afterward the sputum was found to be positive for acid-fast organisms. A repeat film taken 1 month later revealed complete resolution of the process in the right upper lobe but no change in the tuberculosis of the left upper lobe. At this point the patient left the hospital against advice, and contact with him was lost.

Comment. This case most nearly approaches the type of case sought for — active tuberculosis with superimposed pneumococcal pneumonia, with resolution of the latter and continuation of the active process of tuberculosis. Such cases are the best ones for the study of the two diseases, since they show simultaneous occurrence in the same patient. They clearly demonstrate the occurrence of pneumonia with tuberculosis, but the difficulty in finding such cases just as clearly demonstrates the rarity of the situation.

* * *

In all the above case reports, the sputum studies for tubercle bacilli were made by study of the stained smear of the concentrate of a twenty-four-hour specimen.

NIGHT CRAMPS IN YOUNG MEN

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IT WAS with considerable surprise that we found many young men at an Army Air Force installation who were reporting to the dispensary because of distressing night cramps, since this condition is one usually seen in middle-aged and old people. In the course of nine months, 35 men presented themselves for treatment; in 23 of these cases we are reporting our findings. The remaining 12 patients could not be followed or did not return for a checkup.

Night cramps present a fairly typical clinical picture. It is usually that of a person free of symptoms during the day, whether resting or walking. He retires without symptoms but is awakened by a cramping pain in one or both legs. The calf muscles are hard and tender. These muscles are the ones usually affected, but any muscle group in the lower extremity may be involved. Very rarely muscle groups in other parts of the body are affected. Vigorous rubbing of the leg or hopping about gradually relaxes the muscles, but there is often a residual soreness lasting for hours. Attacks may occur once during the same night or frequently.

The patients are often seen in the Vascular Clinic because they are erroneously considered to be suffering from intermittent claudication, but the differentiation is simple, and they almost invariably have no peripheral arterial disease. In this series there were 2 patients with pathologic changes in the veins that appeared to be responsible for the attacks of cramps.

Comparatively little investigation of this subject has been done. Gootnick,[1] having studied 30 cases of night cramps in veterans of World War I, has offered an explanation of the causative factors. It is his belief that night cramps are caused by a tetanic contraction of a muscle group due to reflex bombardment of the myoneural junction by a stream of impulses from some neighboring source of irritation. This source may be arthritis of the hip or knee, weak feet or intrinsic inflammatory changes in the nerves or muscles of the extremities. Gootnick thinks that this reaction represents a variety of segmental visceromotor reflex, similar to that seen in visceral inflammation in the abdomen with resulting abdominal rigidity. In night cramps the irritative focus in the spinal cord is not produced by visceral disease but by the changes in the skeletal structure of the same segmental distribution as the muscles affected.

Gootnick also presents an explanation for the occurrence of cramps at night, based on the physiologic fact that the tension of muscle fibers increases as the muscle lengthens and that beyond a certain degree

of lengthening muscle acquires the tendency to recoil into spasm. During the day, with the patient in the erect or sitting posture, the calf muscles maintain a considerable degree of tone and are in a state of partial contraction against varying degrees of pull. In the recumbent position, however, relaxation and lengthening occur. In muscle already abnormally stimulated by impulses radiating from an irritated segment of the spinal cord lengthening of the muscle constitutes a trigger mechanism sufficient to throw it into spasm. This, Gootnick points out, is nothing more than an exaggeration of the stretch reflex, which is used every time an ankle jerk is elicited by tapping the Achilles tendon. Many patients volunteer the information that they can bring on an attack by extending their legs.

In 1937, Kennedy and Wolf[2] described the use of quinine for muscle spasm in myotonia. In 1940, Harvey[3] pointed out that quinine increases the refractory period of muscle fibers and by reducing the irritability at the myoneural junction decreases the number of stimuli that can reach the muscle fibers. The precise nature of the action of this drug and its relation to acetylcholine and choline esterase remain to be determined. The therapeutic value of quinine in myotonia congenita prompted Moss and Herrmann[4] to use it for the abolishment of night cramps. Later, Gootnick used it in his series of cases. These are the only reported cases to be found in which this drug was used in the treatment of night cramps. Prior to its employment, calcium salts were generally given. It is difficult to conceive why deficiency of calcium should give localized cramps as seen in this condition. In 2 cases of the present series blood-calcium and blood-phosphorus determinations were within normal limits.

Because of the rarity of this condition in young men, it was decided to investigate these 23 cases to determine the age incidence and compare it with that of previously reported cases, to ascertain pathologic changes existing in this group, and to learn the effect of quinine sulfate as a therapeutic agent.

The average age of these patients was twenty-four years. Moss and Herrmann reported 15 cases of night cramps seen in the Vascular Clinic of the Cincinnati General Hospital. No age tabulation was given, but in 4 cases the ages were fifty-seven, sixty-seven, sixty-nine and sixty-nine. In Gootnick's series the great majority of patients were in the fifth, sixth or seventh decade, and the youngest patient was thirty-eight years old. So far as can be determined these are the only reported series, although isolated cases have been commented on in the literature from time to time.

The installation at which this study was done was utilized for the basic training of troops and for the training of aviation mechanics. Their curriculum included considerable marching and drill, physical training and long hours of standing while at school. No Negro soldiers were included in this series.

There were 2 cases of old, deep, venous thrombosis, 1 of old fracture of the right femur with anterior bowing, 12 of static foot deformity and 8 cases in which no disease could be found. In none of the cases was there any evidence of arterial disease. It was also interesting that many of the patients with static foot deformity presented no symptoms directly referable to it. Table 1 summarizes the duration of symptoms, their location, the incidence of occurrence, the existing pathologic changes and the response to quinine sulfate.

Two patients (Cases 19 and 20) were hospitalized for study. The former had had pneumonia three and a half years prior to admission, complicated by deep thrombophlebitis of the left leg, requiring bed rest for a number of months before resuming activity. Within a few weeks he began to develop typical night cramps in the muscles of the left calf, occurring practically every night. When he rested a good deal he had no cramps. At the time of his induction some eighteen months previously, he had noted the appearance of dilated veins on the lower abdomen and left upper thigh. Since that time the veins in the left leg and upper abdomen had become larger and the cramps occurred three to four times a night. Examination showed dilated upper thigh and lower abdominal veins, but no edema of the extremities. The patient was placed at complete bed rest, and after three days noted complete disappearance of his cramps. Bed rest was continued for three more days, without recurrence. He was then allowed up, and the cramps recurred within forty-eight hours. Quinine sulfate given in an increasing daily dosage of 0.20, 0.32 and 0.50 gm. relieved but did not abolish them.

In Case 20, the patient had had pain in both legs and calf muscles for three years; it developed after extensive standing. Thirteen months before admission he began to have severe night cramps in both calf muscles. Examination revealed a contraction of the hamstring and gastrocnemius muscles and second-degree pes planus. The patient had used orthopedic appliances for his feet, without relief.

He was placed at complete bed rest, with disappearance of the night cramps on the third day and without recurrence during the next three days of rest. On being allowed up he had a recurrence on the second day. Quinine sulfate in doses up to 0.50 gm. at night partially relieved but did not abolish the cramps.

The purpose of placing these patients at complete bed rest was to remove the sources of irritation, which brought relief. This tends to support Gootnick's contention that an irritative source is the primary factor in production of the reflex phenomenon resulting in tetanic contraction of the calf muscles.

In this series we first prescribed 0.20 gm. of quinine sulfate, but later this dose was increased to 0.32 gm., since the larger dose was found to be more

practical. In this way it was possible to treat from the start those who required more than the 0.20-gm. dosage, and since men on this post were constantly being moved, it afforded a somewhat longer period to observe the effect of adequate dosage. The medication was taken at night, before retiring. No other medications were used.

No attempt was made to correct static foot deformities, and the patients who used orthopedic appliances were allowed to continue them. Those who had varicosities were given no surgical or other treatment for relief. All the men were informed that they were to keep up their normal activities. The 2 hospitalized cases were followed prior to admission, and the results listed are those secured prior to hospitalization. All the patients were told to report in one week and were instructed to discontinue medication on relief of the cramps and to report the number of days of medication required for this result.

The patients were classified in three groups, depending on the response to quinine sulfate.

Group 1 (17 cases) included those who obtained complete relief; Group 2 (3 cases) included those who obtained partial relief; and Group 3 (3 cases) included those who obtained no relief.

All those who responded well to quinine did so within a period of seven days of medication. Four patients in Group 1 had a recurrence of symptoms within two weeks after stopping the medication. In those who could not be followed for longer periods it was not possible to determine the incidence of recurrences. Five patients followed for one month and 1 followed for two months remained asymptomatic. In the cases in which there was a recurrence, relief was obtained in each case when quinine sulfate was again given.

Three patients in Group 2 obtained only partial relief, but the night cramps became less intense and less frequent. Increasing the dosage had no added effect.

TABLE 1. *Summary of Data.*

Case No.	Age	Pathologic Change	Involvement*	Duration	Frequency	Initial Dosage of Quinine	Results
	yr.					mg.	
				Group 1			
1	37	Old left thrombophlebitis	Left	16 yr.	Nightly	0.32	Relief after 5th dose; no recurrence in 1 month.
2	24	First-degree pes planus	Bilateral	2 mo.	Nightly	0.32	Relief after 2nd dose; no recurrence in 1 month.
3	18	First-degree pes planus	Bilateral	2 yr.	Nightly	0.20	Relief after 1st dose; no recurrence in 2 months.
4	27	Old fracture of right femur with anterior bowing	Right	4 mo.	Nightly	0.20	No relief in 1 week; dosage increased to 0.32 gm., with relief after 3rd dose; no recurrence in 2 weeks.
5	32	Third-degree pes planus	Bilateral	1 yr.	Nightly	0.20	Relief after 7th dose; one slight attack in next 3 weeks.
6	24	First-degree pes planus	Bilateral	3 mo.	Nightly	0.32	Relief after 3rd dose; no recurrence in 2 weeks.
7	28	None	Bilateral	5 yr.	Nightly	0.32	Relief after 5th dose; no further checkup.
8	19	None	Bilateral	2 yr.	Nightly	0.20	Relief after 3rd dose; no recurrence in 1 month.
9	19	None	Bilateral	2 yr.	Nightly	0.32	Relief after 6th dose; no recurrence in 3 weeks.
10	22	None	Bilateral	5 mo.	Nightly	0.20	Relief after 4th dose; no recurrence in 1 week.
11	23	None	Bilateral	3 mo.	Nightly	0.20	Relief after 5th dose; no recurrence in 1 month.
12	19	None	Bilateral	3 mo.	Nightly	0.32	Relief after 2nd dose; no further checkup.
13	25	None	Bilateral	3 yr.	Nightly	0.32	Relief after 4th dose; no further checkup.
14	19	Third-degree pes planus	Bilateral	3 yr.	Nightly	0.20	Relief after 4th dose; recurrence in 2 weeks, resumption of dosage brought relief after 5th dose; no recurrence in 2 weeks.
15	18	Second-degree pes planus	Bilateral	10 mo.	Nightly	0.20	Partial relief after 1 week; dosage increased to 0.32 gm., with complete relief after 5th dose; no recurrence in 2 weeks.
16	27	Second-degree pes planus	Bilateral	5 yr.	Nightly	0.20	Partial relief after 1 week; dosage increased to 0.32 gm., with complete relief after 4th dose; no recurrence in 2 weeks.
17	33	Metatarsalgia	Bilateral	3 wk.	Nightly	0.32	Relief after 5th dose; recurrence 7 days later; dosage decreased to 0.20 gm., with relief after 5th dose; no recurrence in 2 weeks.
				Group 2			
18	24	None	Bilateral	5 mo.	Nightly	0.20	Partial relief; dosage increased to 0.32 gm., then to 0.49 gm., without further effect.
19	23	Old left thrombophlebitis	Left	3 yr.	Nightly	0.20	Partial relief; dosage increased to 0.65 gm., without further effect.
20	33	Second-degree pes planus; tight hamstring and calf muscles, bilaterally.	Bilateral (calf and thigh)	13 mo.	Nightly	0.20	Partial relief; dosage increased to 0.65 gm. without further effect.
				Group 3			
21	18	Second-degree pes planus	Bilateral	5 mo.	Nightly	0.20	No relief after 7th dose; dosage increased to 0.49 gm., without relief after 3 weeks of medication.
22	21	First-degree pes planus	Bilateral	1 yr.	Nightly	0.32	No relief; dosage increased to 0.65 gm., without relief after 2 weeks of medication.
23	25	Second-degree pes planus	Bilateral	3 mo.	Nightly	0.32	No relief; dosage increased to 0.49 gm., without relief after 3 weeks of medication.

*Unless otherwise indicated refers to calf muscles.

Despite increased dosage those in Group 3 obtained no relief, although medication was continued for a number of weeks. We believed that increasing the dosage of quinine above 0.32 gm. or continuation of the medication for longer than ten days was not indicated if relief was not obtained in that time.

No definite correlation could be found between the underlying pathologic changes and the response to medication. In Group 1 there were 7 patients in whom no pathologic changes could be found, whereas there was only 1 such patient in Group 2, and none in Group 3. In general one might expect a better therapeutic response in these subjects.

Discussion

In contrast to the results obtained by Gootnick, 26 per cent of these patients failed to obtain complete relief from night cramps by the use of quinine sulfate, and the majority of those who obtained relief required a number of doses. The effect of this drug is short-lived and not cumulative, and we are unable to explain why patients should have relief for many days, and not infrequently for weeks, after medication had ceased.

In slightly more than a third of the cases no underlying changes could be found, which raises a question concerning the occurrence of night cramps in apparently normal persons. It may be that these men had lowered muscular strength and general muscular weakness not obvious on routine physical examination or a lower threshold of irritability induced by fatigue from the training program. They were able, however, to keep up with the rest of the troops and to carry on the usual daily routine. No difference could be seen between their general physical makeup and that of the average healthy soldier. No attempt was made to judge physical endurance or muscular capacity by means of physical-training gradients.

The most frequent disorder predisposing to night cramps was static foot deformity, which occurred in 12 cases. Five of these patients also had symptoms directly referable to the feet. In all these cases orthopedic appliances had been used, with partial relief of foot symptoms but with no change in the occurrence of the night cramps. In none of the patients was there found any peripheral arterial disease, although in 2 cases there was old deep thrombophlebitis of the lower extremities.

Summary and Conclusions

Night cramps occur in young men as well as in older people.

Static foot deformity appeared to be the most frequent single predisposing factor in the occurrence of night cramps in this series.

Apparently healthy persons may have night cramps, and yet physical examination may fail to show any defects.

Quinine sulfate offers rapid and frequently complete relief, for varying periods, in a majority of cases.

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MEDICAL PROGRESS

THE EFFECTS OF INFECTION ON THE CIRCULATION*

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THERE are many ways in which infection may give rise to circulatory disturbances, and it is the purpose of the present report to discuss the pathologic physiology of these disorders.

A large number of infectious diseases, some still of doubtful etiology, give rise to vascular lesions. Included in this group are rheumatic fever, syphilis, Fiedler's myocarditis, acute disseminated lupus erythematosus, periarteritis nodosa, mycotic aneurysms, acute and subacute bacterial endocarditis, typhus fever and meningococcemia. Similarly, the various urticarias, purpuras and macular or papular rashes also represent the effects of vascular lesions. It is not our purpose to describe the pathologic anatomy of any of these; it is sufficient merely to call attention to the fact that some infections give rise to anatomic changes involving the cardiovascular system. A functional disorder of the cardiovascular system that may occur in association with infectious processes is arrhythmia of the heart. The heart block of diphtheria, the prolonged PR interval of rheumatic fever and other infections and the transitory auricular fibrillation associated with pneumonia in the aged are too well known to require emphasis in the present work.

Fever

Another way by which cardiovascular physiology may be influenced during the course of infectious processes is through the occurrence of fever. Although the importance of fever as a symptom of infectious disease has been known since the time of Hippocrates, appreciation of the physiologic mechanisms that result in the circulatory and respiratory manifestations of fever is not widespread among clinicians. Studies of fever consequent on the intravenous injection of killed typhoid bacilli or live malarial parasites[1, 2] make it clear that the febrile reaction consists in phases that are fairly sharply defined and that follow in regular sequence. The clinical appearance of the patient is distinctive, and the various cardiorespiratory functions that have been measured likewise show different changes in each phase. The phases have been termed "prodrome," "chill," "flush" and "defervescence."

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The prodrome begins soon after the endovenous injection of the typhoid vaccine, lasts thirty to ninety minutes and is characterized by lassitude, headache, generalized aches and pains, and malaise. Measurements of cardiac output, venous pressure, circulation time, pulse rate, blood pressure, vital capacity, respiratory rate, oxygen consumption, respiratory minute volume, respiratory quotient, arterial and venous oxygen and carbon dioxide content, arterial pH and blood volume show no significant changes from control values; electrocardiographic tracings reveal no deviation from the normal. Direct observation of the cutaneous capillaries in the fingernail bed shows no changes in caliber or flow.

The mechanisms responsible for the prodromal period and the symptoms observed are not understood. Although it is assumed that antigen-antibody reactions are probably taking place, no clear evidence exists for their presence. In this connection it should be mentioned that many observers have induced fever in animals and in human subjects with purified proteins or polysaccharides obtained from bacteria or exudates.[3–7] In all these instances a prodromal period is present.

The chill phase begins suddenly. The patient becomes pale and cyanotic, and goose flesh may be observed. The skin is, however, dry except that a few beads of perspiration become visible on the forehead or upper lip. The superficial veins become visibly narrow, and withdrawal of blood from them may be difficult. Obvious hyperventilation occurs. Nausea is a complaint in almost all patients, and some vomit. Excretion of urine is minimal or absent during this phase. The rectal temperature rises rapidly but the skin remains cool. The patients complain of feeling cold and many shiver; in some cases severe shaking chills occur. The latter can be precipitated in the chill phase by exposing the patient to a blast of cool air or by placing a small piece of ice in his hand. Conversely external heat and blankets minimize the shivering of the chill. The dynamic changes occurring during the chill phase last from one to two hours. The capillaries of the nailfold rapidly disappear, and the few that remain visible are markedly narrowed and contain blood that moves slowly. The columns of blood within the capillaries appear segmented. The systolic and diastolic levels of arterial blood pressure tend to rise in the early part of the chill phase, but in some cases, a marked fall in blood pressure

occurs, a point that will be discussed further below. The antecubital venous pressure, measured directly, usually shows no striking change, but a fall in venous pressure occurs in some cases. The arteriovenous oxygen difference increases during the chill phase, with a marked fall in venous blood oxygen content. Changes in cardiac output are variable in the chill phase; the cardiac output often falls, whereas in the remainder of the cases the increases in cardiac output are smaller than what would be expected from the observed changes in oxygen consumption. Slowing of the arm-to-tongue circulation time occurs in almost all patients during the chill phase, the degree of slowing varying with the severity of the chill reaction. The pulse rate rises approximately ten beats per minute for each degree rise in rectal temperature.[8–10] When rigors or muscle tensing is absent, the oxygen consumption varies roughly with the rectal temperature, increasing approximately 7 per cent for each degree of fever.[11–13] The respiratory minute volume rises during the chill phase, the increase exceeding that of oxygen consumption. The increase in respiratory rate, greater than that of the minute-volume respiration, results in a decrease in tidal air. The alveolar-air carbon dioxide content and the arterial carbon dioxide level fall during the chill phase, and the arterial blood pH rises slightly. The respiratory quotient is increased.[1, 13] In severe chill reactions, an increase in residual air may be observed, indicating some degree of pulmonary congestion. A fall in reserve and complemental air and in vital capacity is seen in such cases. Changes in the oxygen saturation of the arterial blood, however, are small. The blood volume is unchanged.[1, 14] Aside from the observed increase in pulse rate, the electrocardiograms showed flattening of the T waves late in the chill phase.

It is apparent from these observations and from others in the literature that the chill phase is associated with the onset of marked generalized vasoconstriction, which is visible in the skin and nailfold capillaries and is also probably present in the kidneys and brain. In 1883 Mendelson[15] demonstrated during fever in dogs a progressive shrinkage in the size of the kidneys, which he attributed to arterial constriction, and Fremont-Smith et al.[16] showed that the chill phase induced by typhoid vaccine, malaria and rat-bite fever was associated with a cessation of urine formation. Recently, Smith et al.[17] showed that the chill phase of typhoid-vaccine fever is accompanied by a 25 per cent reduction in renal blood flow. It is of interest that the previous administration of pyramidon abolished the febrile reaction but did not prevent the renal vasomotor changes. The studies of Himwich et al.[18] showing an increased arteriovenous oxygen difference in cerebral blood, suggest that the brain participates in the circulatory stagnation of the chill phase. Since the circulating blood volume shows no change, it is apparent that there must be areas in the body that are not the seat of generalized vasoconstriction and may be the site of vasodilatation. The increase in the residual air volume and in the ratio of the residual air to the total pulmonary capacity in the chill phase suggests that some degree of pulmonary congestion may occur. It is of some interest in this respect that Sprunt and Camalier[19] have shown the occurrence of edema and congestion of the lung of rabbits and men following the injection of staphylococcal and other toxins. That the observed vasoconstriction is nervous in origin is apparent from the studies of Johnson, Osborne and Scupham[20] and Perera,[21] who observed no vasoconstriction in a denervated limb. In 1927, von Euler[22] described a substance in the blood of patients with fever that had vasoconstrictor effects and also gave colorimetric reactions suggesting that it was adrenalin. It should be stressed that the observed changes in skin circulation in the chill phase are the same as those that occur with externally applied cold; thus, the cutaneous vasoconstriction of exposure to cold is associated with narrowed veins, a decreased rate of circulation, a decreased oxygen content and a fall in skin temperature, which, when it reaches a sufficiently low level,[23] results in shivering or muscle tenseness. Furthermore, with the increased heat production and the inability to lose heat through the skin, the internal body temperature rises. The severer the chill, the greater the rise in body temperature. Once the circulating blood within the skin and brain rises to a certain level, relaxation of local vasoconstriction and central stimulation of vasodilator fibers occur, which ushers in the flush phase.

The observed decreases in cardiac output are probably not related to a direct depression of cardiac function, since bradycardia does not occur, and since the tachycardia of fever ordinarily does not reach levels, that is, 180 per minute or above,[24] that might give rise to a lowering of cardiac output by markedly shortening diastole. Furthermore, measurements of the venous pressure never show an increase. Thus the changes observed in cardiac output during the chill phase are a resultant of the tendency to rise with the increasing oxygen consumption and the tendency to fall with the impairment of venous return that is probably present. The changes in circulation time are probably related to cutaneous vasoconstriction, since Stead and Kunkel[25] have shown that simple cooling of the skin may comparably slow the arm-to-tongue circulation time.

The mechanisms responsible for the excessive hyperventilation of the chill phase are as follows: limitation of heat dispersal due to cutaneous vasoconstriction; increased temperature within the brain, which is known to give rise to hyperventilation,[26–28] the latter being a mechanism for heat dispersal; anoxia, which occurs when the cardiac output falls; and pulmonary congestion, which

may activate reflexes within the lungs, thus producing excessive hyperventilation. The observed hyperventilation is responsible in part for the rise in the respiratory quotient, although the probability exists that an increase in carbohydrate utilization with increased fever may be a factor. The alkalosis that results from the observed hyperventilation may be responsible for the occurrence of convulsions in children; the fact that the alkalosis is not marked is probably due to the observed elevation of fixed acids, namely, lactate and pyruvate, within the blood.[29]

The flush phase of the febrile reaction is characterized by the rapid development of a generalized flush and a drenching sweat. The patient suddenly complains of feeling warm, and the skin is hot; the superficial veins become markedly dilated. A pounding headache occurs, and complete relief of nausea and vomiting is noted. The onset of the flush phase is usually associated with a diuresis. This phase lasts for approximately one hour and then passes into the phase of defervescence, the abnormal findings in the flush phase gradually regressing over a period of several hours.

The physiologic changes in the flush phase are manifold. There is a rapid appearance of large numbers of widely open capillaries in the fingernail beds, containing blood moving rapidly. All visible vessels, including arterioles and venules, appear to pulsate. The arterial blood pressure, both systolic and diastolic, shows a fall, but the venous pressure remains unchanged or rises a little. The circulation time is uniformly decreased, and the cardiac output increases markedly and in excess of what would be accounted for by the observed increase in oxygen consumption. As a consequence, the arteriovenous oxygen difference falls, and the venous oxygen content rises almost to the arterial level. The respiratory minute volume increases, but the respiratory volume relative to oxygen consumption per minute falls to or toward normal. The rate of respiration decreases somewhat, as compared to the respiratory minute volume, and the tidal-air volume usually increases. The alveolar-air carbon dioxide content remains low, and the arterial pH remains elevated; both return toward control levels during defervescence. The blood volume is unchanged. Electrocardiograms taken during the flush phase usually show inversion of T waves, unassociated with changes in the ST segment.

The marked generalized vasodilatation initiated in the flush phase probably involves not only the capillaries but also the arterioles and arteriovenous shunts. The latter is likely, since venous blood becomes arterialized and slight rises in venous pressure are observed. The excessive increases in cardiac output are probably related also to opening of arteriovenous shunts, with an increased venous return, and perhaps also to elevated cerebral temperatures.[27] Nevertheless, there must be areas of compensatory vasoconstriction, since the blood volume is not changed.

The sudden vasodilatation observed in the flush phase probably involves a neurogenic mechanism, activated by increased warmth of the blood within the brain, with resultant stimulation of vasodilatation centers. Gibbon and Landis[30] have shown that increased temperature of the blood within the brain produces a generalized vasodilatation; furthermore, a sympathectomized extremity does not exhibit vasodilatation when the body is heated. It is of interest that Hewlett[31] has shown that a previously chilled extremity, when warmed, does not show an increased flow until the external temperature has been considerably elevated. It is thus possible that the local circulation of sufficiently warm blood may relax vasoconstriction. The elevation of pulse rate is probably due to increased warmth of the blood supplying the sinoauricular node,[32], [33] although the possibility exists that central stimulation is a factor.[26]

The duration and severity of the four phases of a febrile reaction may vary greatly in various infectious diseases. Thus, in a patient with untreated pneumococcal pneumonia, the moderately severe chill phase of a few hours may be followed by a flush lasting more than a week, this being in turn followed by defervescence over a period of a few hours or a few days. In typhoid fever, on the other hand, a prodromal period of one to two weeks may occur, followed by a week of successive elevation and partial lowering of temperature, which may be compatible with many chill and flush phases, followed by a long flush period of several weeks. In a patient with a septic process or malaria, severe chill and flush phases of approximately equal duration may occur daily. It is apparent that, under these circumstances, many factors as yet not understood unquestionably modify the above described manifestations of the febrile reaction.

Thiamine Deficiency

The development of thiamine deficiency in patients with infectious diseases of long duration is well known. Accordingly, the circulatory manifestations of fever may be modified by the changes in cardiovascular dynamics consequent to vitamin B_1 deficiency. The available data,[34] although scanty, suggest that thiamine deficiency in man is associated with a relative increase in cardiac output as compared to the oxygen consumed, a decrease in the circulation time, an increase in the oxygen consumption, an increase in the circulating blood volume and an elevated venous pressure. There is a decreased arteriovenous oxygen difference, and with the decreased circulation time, there is thus suggested the presence of an abnormally dilated peripheral vascular bed. The cardiovascular changes of the chill phase of fever might be somewhat diminished, whereas the phenomena of the flush phase

might tend to be accentuated in the presence of thiamine deficiency. In addition, a deficiency of this vitamin resulting from a protracted infection might give rise to congestive heart failure.

Anemia

Severe anemias not infrequently develop during the course of infectious disease. Anemias increase the cardiac output, lower the arteriovenous oxygen difference and accelerate the circulation time. Anemia therefore superimposes an additional strain on the heart beyond that caused by fever. It should be noted in addition that anemic patients show cutaneous vasoconstriction, probably of sympathetic origin, and that patients with pernicious anemia or indeed any severe anemia frequently present elevations of body temperature.

Congestive Heart Failure

The burden placed on the heart by fever may, after a time, cause a previously damaged heart to fail. The contributing roles of anemia and thiamine deficiency have already been noted. The development of signs of myocardial insufficiency during infections in elderly or cardiac patients is well known. All patients in uncomplicated congestive failure exhibit peripheral vasoconstriction, with consequent impairment of heart dispersal, and indeed some such patients exhibit slight elevations of body temperature. This impairment of heat dispersal through the skin may give rise to severe dyspnea in the presence of fever. It is of interest that Buchbinder and Saphir[35] observed the pathologic changes of congestive heart failure in approximately half of a large series of patients with subacute bacterial endocarditis.

Rashes

The vasomotor manifestations of fever are of interest in relation to the occurrence of disappearance of erythematous rashes. Thus the cutaneous vasoconstriction of a severe chill may cause a rash to disappear or become darker in hue. On the other hand, an extremely severe flush may mask a macular erythema to some extent.

Postinfectious Asthenia

It is a striking clinical observation that patients who have recovered from short febrile illnesses may be excessively weak and tired. They often exhibit profuse and easy sweating and such marked vasomotor instability that postural syncope occurs. These symptoms may last for considerable periods of time and may be far more incapacitating than the illness that they followed. Although the cause of this postinfectious syndrome has not been completely elucidated, certain of the phenomena are explainable. It is known that fever causes certain biochemical changes similar to those of trauma, myocardial infarction and burns, that is, a markedly negative nitrogen balance and creatinuria[36–38]; these changes may be associated with obvious muscular wasting. It is also apparent from the data cited above that a febrile illness gives rise to a considerable degree of stress on the centers controlling vasomotor, cardiomotor, respiratory and sweating functions, which might result in prolonged instability in the function of these centers.

Infectious Shock

Shock consequent to trauma and hemorrhage has been widely investigated, but few data are available in shock due to infection. The clinical manifestations of shock, whatever the etiology of the latter, are more easily recognized than described. The appearance of the patient in shock associated with an infection is similar to that of the patient in an extremely severe chill phase; one difference between the two is the fact that the rectal temperature rises during the chill phase of fever, whereas it may not rise, and indeed may fall to subnormal levels, in infectious shock. It is of interest that shock in infections occurs early in the course of the disease: for example, patients with meningococcemia may develop peripheral vascular collapse before signs of meningitis have appeared.[39, 40] Shock may likewise be the presenting symptom in postoperative wound infections,[41] peritonitis,[42] acute bacillary dysentery,[43] scarlet fever,[39] and acute pneumococcal pneumonia.[39] In addition, the studies of Aub et al.[44] and of Prinzmetal et al.[45] suggest that shock due to tourniquets or crush injury in dogs may be largely consequent to infection. A large volume of clinical data based on observation of patients and also on the response to digitalis bodies and to fluids and various sympathomimetic substances has convinced clinicians that infectious shock is not related to cardiac failure but to some disturbance of the peripheral circulatory apparatus.

Measurements of circulation. As mentioned above, the clinical picture of shock develops in some patients during the chill phase of the febrile reaction to typhoid vaccine. This is associated with a low cardiac output, an increased arteriovenous oxygen difference, deoxygenation of the venous blood and a low arterial blood pressure. The circulating blood volume is unchanged, however, and oxygen consumption and rectal temperatures do not fall. It is pertinent to point out that the cutaneous manifestations of vasoconstriction — that is, cold,clammy extremities, blanched mucous membranes, cutis marmorata and venous constriction — are present in the chill phase of the febrile reaction as well as in infectious shock. In both instances these phenomena are neurogenic in origin. In patients with infectious shock, ulnar-nerve block with procaine results in increased warmth of the involved fingers.[46] Many years ago Freedlander and Lenhart[47] described capillary constriction and slowed flow in the skin of the nailfold of patients in shock consequent to

infection. Ebert and Stead[46] studied 8 cases of circulatory failure in infections, 6 of which were due to pneumococcal pneumonia. In none was the circulating plasma volume significantly altered. The absence of elevation of venous pressure rules out a primary cardiac failure.[46] Eppinger and Schürmeyer,[48] on the other hand, noted a decreased circulating blood volume in infectious shock. The observations of Rutstein et al.[49] on the plasma volume and the so-called "extravascular thiocyanate space" in pneumonia show an increase in these values during the illness, with a decrease below normal immediately following recovery. In fatal cases the values were significantly lower than in the patients who survived. These workers correlated the lowered plasma volume with the clinical occurrence of peripheral circulatory failure. The difference in methods employed is not sufficient to explain these discordant results.

Studies have been made of the cardiovascular dynamics consequent to the intravenous injection of various bacterial toxins in unanesthetized dogs.[3] The clinical appearance of these dogs resembled closely the shock state, pallor of the mucous membranes, narrowed veins, hyperventilation, anuria, insensibility to pain and general apathy having been observed. Within fifteen to thirty minutes after the injection of Shiga toxin, a decrease in cardiac minute volume output of 25 to 75 per cent occurred. This change was associated with an increased arteriovenous oxygen difference, marked deoxygenation of the venous blood and a concomitant decrease in the right auricular pressure; the portal venous pressure, however, rose. The latter change was probably due to spasm occurring in the hepatic veins,[50] with a resultant decrease in venous return from the splanchnic bed, but it is unlikely that this mechanism exists in human beings. The arterial blood pressure was maintained, indicating peripheral vasoconstriction, and evidence of hemoconcentration was absent. During the succeeding hours, despite at times considerable rises in body temperature and severe shivering, the cardiac output persistently decreased and the circulation time became greatly slowed. The portal venous pressure fell to levels considerably below control values. The oxygen consumption increased parallel to the rising body temperature, but both fell when the animal was in deep shock. Decreases in blood volume and increases in viscosity became manifest in two thirds of the dogs late in shock. The late blood-pressure changes were variable. In some animals, the blood pressure rose with the rising body temperature, until the latter reached its peak, when a precipitous fall in blood pressure occurred. It is apparent from the data given above that in these animals vasodilatation associated with the flush phase had set in. In others, a fall in blood pressure to 40 or 50 mm. occurred after one or two hours. This is a counterpart of the fall in blood pressure observed in the chill phase of some human experiments. It should be noted in this regard that recently Warren et al.[39] described 3 cases of infectious shock that illustrate perfectly this type of reaction. Their conclusion that the mechanism of shock is related to a pooling of blood in dilated capillaries, and therefore an uncompensated increase in the size of the vascular bed, with a concomitant reduction in venous return to the heart and in cardiac output, implies that there was a decrease in circulating blood volume. The studies of Ebert and Stead[46] and our [1, 2] observations, both in human beings and in animals, do not support this conclusion.

Comparison of circulatory dynamics in infectious shock and in shock due to trauma and hemorrhage. Toxic or infectious shock is similar to experimental traumatic and hemorrhagic shock in the occurrence of a fall in cardiac output and central venous pressure, an increase in the arteriovenous oxygen difference, a marked fall in the venous oxygen content, a slowing of the circulation, a decrease in oxygen consumption, a fall in the arterial blood pressure and an early increase, followed by a late fall, in peripheral resistance. Toxic or infectious shock differs from traumatic or hemorrhagic shock in two respects: the occurrence of fever, with its specific effects on blood pressure, cardiac output and oxygen consumption, and the fact that oligemia is not the initiating mechanism in at least some types of infectious shock. The occurrence of the latter, whether due to dehydration or loss of plasma or blood, is of serious consequence in infectious shock.

Factors influencing occurrence of infectious shock. The occurrence of severe diarrhea in cholera, bacillary dysentery, ulcerative colitis and so forth may induce such dehydration and contraction of the circulating blood volume that they are of considerable significance in the precipitation of shock. Whether the cardiovascular dynamics in such patients differ from those observed in nonoligemic shock is not known.

Andrews and Harkins[51] measured the weight of pneumonic lungs and concluded that sufficient plasma and blood is lost to account for the occurrence of shock on an oligemic basis. As has been pointed out above, measurements of the circulating blood volume in shock and pneumonia have presented conflicting results. Other examples of rapid loss of plasma in infections are offered by phlegmonous areas and pleural empyema. It should be noted that, although the amount of plasma loss alone may not be sufficient to account for the induction of shock, it is certainly a deleterious factor.

In 1920 Lautenschläger[52] analyzed the effects of the intravenous injection of unconcentrated filtrates of cultures of *Clostridium septique* and concluded that the circulatory collapse so induced was due to a cardiotoxic digitalis-like effect of the toxin. More recent studies by other investigators have

demonstrated a toxic effect on the heart, as well as constriction of the pulmonary and coronary vessels.[53] Studies on staphylococcal[54, 55] and streptococcal[56] toxins likewise show a direct cardiotoxic action. Bernheimer and Cantoni[56] suggest that the cardiotoxic factor of *Streptococcus pyogenes* is closely related to and perhaps identical with the oxygen-labile hemolysin of the streptococcus. In all the above experiments enormous doses of toxin were used. On the other hand, in dogs in shock after the intravenous injection of Shiga toxin, the administration intravenously of large infusions resulted in a moderate increase in cardiac output and in no abnormal rise in venous pressure[3]; these findings were taken to indicate that the heart responds normally to increased venous pressure. It should be noted, however, that after such infusions the cardiac output did not rise quite to the control value and soon returned to the preinfusion level. In addition, the absence of any beneficial clinical action of digitalis suggests the absence of a significant cardiac factor in infectious shock. That the heart may be damaged by the presence of shock is well established; Blumgart et al.[57] found thrombotic occlusion of the coronary arteries in patients who died of shock due to diverse causes.

The Waterhouse–Friderichsen syndrome is described as an infectious disease, occurring mainly in children, that is characterized by a purpuric syndrome involving the skin and adrenal glands and by a severe and almost uniformly fatal shock. In most of the recorded cases, meningococcal bacteremia has been found, although isolated cases of hemolytic streptococcus, staphylococcal and pneumococcal bacteremia have been described. Rich[58] and others,[59] however, have described adrenal lesions in infectious shock of diverse origin, and hemorrhages within the cortices of the adrenal gland were found at autopsy in many animals injected with the protein fraction of Shiga bacilli.[29] It is to be noted that except for the rash, the clinical picture is not at all unlike severe experimental or clinical infectious shock. D'Agati and Marangoni[60] recently concluded that the difference between meningococcemia complicated by collapse and the Waterhouse–Friderichsen syndrome is the absence in the former of anuria, oliguria and the retention of nitrogenous products. These considerations, however, have no validity, for in every type of peripheral vascular collapse so far studied, and also in the chill phase of fever, renal excretory function practically ceases.

Dale and Evans[61] showed that the activity of the vasomotor center is regulated by the concentration of carbon dioxide in the blood, and it is well known that hyperventilation may cause a transient fall in blood pressure if enough carbon dioxide is blown off. Henderson[62, 63] believed that hypocarbia is an important factor in the genesis of shock. In our experience, however, the degree of hypocarbia necessary to cause significant hypotension is so marked as to rule hyperventilation out as the primary cause of the fall in blood pressure seen in infectious shock.[3] It may possibly be a contributory factor in some cases.

The studies of Porter[64–66] and others[67, 68] show no impairment of the function of the vasomotor center in infectious shock.

Moon[69] has described shock as due to widespread capillary dilatation and increased permeability. The evidence that infections cause increased capillary permeability largely consists of Moon's pathological studies showing visceral engorgement in infectious shock. This type of evidence is inconclusive, since visceral engorgement may be an effect of shock rather than a causative factor. Duran-Reynals[70] reviewed the role of the so-called "spreading factors" in giving rise to local increases in capillary permeability in inflamed areas, and Menkin[71] ascribed these changes to "leukotaxine," a nonprotein nitrogenous substance present in exudates. As pointed out above, however, these phenomena are not important in the genesis of infectious shock unless the inflamed area is so extensive that a large loss of plasma from the circulation results. No conclusive evidence exists that a generalized increase in capillary permeability is present in infectious shock.

Therapy of Peripheral Vascular Collapse in Infection

In general, the therapy of infectious shock is most unsatisfactory, and in almost all fatal cases the patients die of or with shock. Atchley,[72] Eggleston[73] and Warfield[74] have discussed the treatment of this type of shock, and certain general principles should be stressed. The prevention of the development of shock by the early recognition and treatment of disease is of primary importance. If shock is already in evidence when the patient is first seen, the use of adequate amounts of plasma given intravenously is necessary to keep the patient alive long enough for specific serums or antibiotic substances to act; if the latter are not given, plasma infusions have only a temporary beneficial effect. Pressor drugs are ineffective in the presence of infectious shock when given alone,[75] but when used together with plasma, they regain their effectiveness.

Cardiovascular Complications of Treatment of Infection

Symptoms relating to cardiac and vascular function may be greatly modified in a deleterious manner by treatment. Thus, the purpuras and urticarias of antibiotic or other therapy, the anaphylactic reactions of serum therapy and the pulmonary or peripheral edema following infusions may be more alarming than the infections for which they are employed. These complications may be avoided, or at least minimized, by careful treatment. In some cases, induced fever is used to treat low-grade

infections. That produced by physical methods, such as diathermy and hot baths, differs from infectious fever. Not only is there no chill phase, but the flush phase is greatly accentuated, since heat dispersal is usually impaired by a warm environment. The circulatory changes in physically induced fever are similar to those observed in the flush phase of typhoid-vaccine fever, except that a more marked increase in blood flow through the skin is present in physically induced fever. Whereas the blood pressure changes are variable, the peripheral resistance falls. The inability of the patient to lose heat normally results in an increased sweating and in extreme hyperventilation. Thus, dehydration, decreased blood volume[14] and severe alkalosis may result. The extreme hyperventilation may be associated with oxygen unsaturation of the arterial blood.[76] These changes induced by therapy in a patient with a febrile disease have been reported to be associated with the development of shock.[77] The administration of adequate amounts of fluid and, when necessary, oxygen prevents the development of this syndrome.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor**

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CASE 31451

PRESENTATION OF CASE

First admission. A fifty-one-year-old man entered the hospital complaining of shortness of breath.

Two years before admission, after lifting a heavy object, he had an attack of severe dyspnea lasting about thirty minutes. Six months before admission he had a similar attack after undue exertion. Four months later sporadic dyspnea on moderate exertion appeared and gradually became severer. Orthopnea and ankle edema developed. Three days before admission he was seized with a severer attack of dyspnea than he had ever had, and it persisted until admission. Orthopnea, insomnia and a nonproductive cough were present. The abdomen increased markedly in size.

At the age of twenty, and again at thirty-five, the patient had complained for several months of migratory joint pains. He had never had substernal pain or oppression.

Physical examination revealed an obese, cyanotic man sitting upright in bed and breathing rapidly and with difficulty. The chest was barrel-shaped, and rales were heard throughout both lungs. Percussion of the heart was unsatisfactory. Over the aortic area and along the left border of the sternum a soft, early diastolic murmur was heard. A soft systolic murmur was heard over the aortic area. The sounds were distant and of poor quality. Frequent extrasystoles were heard, but they were too weak to cause any irregularity of the pulse. The abdomen was greatly distended and tympanitic, but no masses or fluid could be detected. The ankles showed moderate pitting edema. The reflexes were physiologic.

The temperature was 101°F., the pulse 60, and the respirations 35. The blood pressure was 160 systolic, 50 diastolic.

Examination of the blood revealed a red-cell count of 6,300,000, with 91 per cent hemoglobin (Sahli), and a white-cell count of 16,900, with 68 per cent neutrophils. The urine was normal. A blood Hinton test was negative. An x-ray film of the chest showed enlargement of the heart, more pronounced to the left than to the right, with slight tortuosity of the aorta. The hilus vessels were moderately enlarged. There was a poorly defined homogeneous dullness of ground-glass appearance occupying the lower two thirds of the medial portion of both lung fields. An electrocardiogram showed auriculoventricular block (usually 2:1), with occasional sinoauricular block.

Profuse diuresis was obtained after the administration of Mercupurin. The patient was discharged improved on the twentieth hospital day, with instructions to take digitalis.

Second admission (five years later). After discharge he was followed in the Out Patient Department, where it was found that his symptoms of congestive failure had almost completely subsided. The pulse rate was about 50 and irregular. Two years later the patient caught cold and noted increased dyspnea. He wheezed and had a frequent cough. He was slightly cyanotic. The heart rate was 100 and regular. The liver was not enlarged. He improved on digitalis. Three years after this examination, exertional dyspnea again became distressing and the abdomen enlarged. He was readmitted to the hospital.

The blood pressure was 170 systolic, 60 diastolic. Rhonchi and wheezes were heard throughout both lungs. There was dullness at the bases. The heart sounds were distant; the rate was 50 and regular. Aortic systolic and diastolic murmurs were present. The abdomen was distended and tympanitic, with a fluid wave. Ankle edema was present. The blood

*On leave of absence.

and urine were normal. The nonprotein nitrogen was 34 mg. per 100 cc. An x-ray film of the chest showed marked enlargement of the left ventricle and prominent vascular markings. There was no free fluid in either base. An electrocardiogram showed a ventricular rate of 60 per minute, with 2:1 auriculoventricular block, left-axis deviation, depressed ST_1, ST_2 and ST_3, inverted T_1, diphasic T_2, upright T_3 and inverted T_4. He was discharged improved on the fourth hospital day.

Third admission (one year later). The patient was followed in the Out Patient Department and remained in good condition until he cut his left foot while paring a corn. Pain, swelling and redness appeared. He was admitted for treatment of the infection, which subsided rapidly. The blood pressure was 210 systolic, 80 diastolic, and auricular fibrillation was present. The feet were cold, and no dorsalis-pedis pulse was detected. He was discharged on the sixth hospital day.

Final admission (seven months later). After discharge, auricular fibrillation continued. Two weeks before his final admission, at the age of fifty-seven, he returned to the Emergency Ward complaining of an itching red rash starting on the forearms and later spreading to the trunk and legs. Linear rows of vesicles were seen on both arms, with swelling and tightness of the skin, and many crusted lesions. There was an erythematous rash in the axillas and on the trunk and legs. The rash subsided within a week, but the swelling persisted. At about that time the patient discontinued digitalis, and four days later he noted swelling of the legs and orthopnea. The quantity of urine decreased. The blood pressure was 200 systolic, 70 diastolic. He was given 1 cc. of Mercupurin intravenously in the Out Patient Department, but he passed only a few drops of urine. Two more cubic centimeters of Mercupurin was administered, but he remained anuric. He was unable to sleep, noted progressively severe dyspnea, orthopnea, swelling of the abdomen and ankle edema and had a loose cough productive of white frothy sputum. There was no hemoptysis, hematuria or pain in the chest or abdomen.

Physical examination revealed an apprehensive, orthopneic and slightly cyanotic man. Dullness and coarse rales were found throughout the lungs. The heart was enlarged about 12 cm. to the left of the midline and 1 cm. to the right of the sternum. A marked precordial thrust was palpable as far laterally as the left midaxillary line. The apical rate was 126, and the radial 63. An aortic systolic murmur was prominent. The skin was tense over a distended abdomen in which shifting dullness could be only questionably demonstrated. The liver was enlarged, being palpable 2 cm. below the right costal margin. There was marked pitting edema of the sacrum and lower legs. The reflexes were sluggish but present.

The temperature was 98°F., and the respirations 25. The blood pressure was 220 systolic, 80 diastolic.

Soon after admission the patient passed about 150 cc. of urine, the first in more than forty-eight hours. It was cloudy, amber and acid in reaction; the specific gravity was 1.019. It gave a +++ test for albumin, and the sediment contained about 100 red cells, 20 to 50 white cells and many hyaline and granular casts per high-power field. It was negative for sugar, acetone and bile. The red-cell count was 4,280,000, and the white-cell count 9200, with 69 per cent neutrophils.

The patient remained dyspneic, orthopneic and apprehensive. The pulse rate became regular at 60. An electrocardiogram showed complete heart block, but no sagging of the ST segments. He was treated with morphine, aminophyllin, ammonium chloride and the Schemm diet, but no more Mercupurin was given. Oliguria persisted. He expired on the third hospital day.

Differential Diagnosis

Dr. Conger Williams: The symptoms leading up to the first admission could represent several things, the likeliest being pulmonary congestion secondary to left-sided heart failure brought on by exertion. Another thing that I thought of but discarded was spontaneous pneumothorax, which may be initiated by effort. That diagnosis does not fit in with later events, however.

The migratory joint pains make it seem quite likely that at some time in his career the patient had had active rheumatic fever. When he was first admitted, there may have been some rheumatic scarring of the heart valves, but not enough to account for the heart failure because the only murmurs described at that time were a soft systolic and a slight diastolic murmur, both in the aortic area, which certainly do not indicate significant mechanical defects. Therefore, other possibilities, such as rheumatic activity, must be considered, as well as pulmonary embolism, often a complication in such a situation. Syphilitic aortitis is suggested by the aortic diastolic blow. Heart failure sometimes follows slow complete occlusion of one of the mouths of the coronary arteries in that disease, but the long duration of heart failure here rules out that possibility. Mitral stenosis might also be considered to explain the long-standing pulmonary congestion, in spite of the absence of the characteristic murmur, which is sometimes difficult to hear in an obese patient. It is unusual, however, for mitral stenosis to produce marked peripheral congestion in the absence of auricular fibrillation except in the course of active rheumatic infection.

May we see the x-ray films?

Dr. Milford D. Schulz: These films cover a period of six years. The first shows a heart apparently enlarged in all diameters, principally in

the left ventricle, and a ground-glass appearance in the central portions of the lung fields, which is quite characteristic of pulmonary edema. A month later the lung fields are clear. The heart remains about the same size.

Four years later the heart was a little larger than it was on the first examination and the hilar shadows were more prominent. An examination within recent months shows the lung fields to be quite clear.

DR. WILLIAMS: Do you think that the heart looks smaller in this last film than it did six years earlier?

DR. SCHULZ: It appears to be, but there may have been a change in technic in the interval. The whole chest appears to be somewhat smaller. Certainly the heart is not larger than it was six years previously.

DR. WILLIAMS: Six years elapsed between the first and the final admissions. During that time the patient did remarkably well, barring an occasional episode of congestive failure. Auricular fibrillation was observed during the third hospital admission and apparently remained the dominant rhythm until death.

At the time of the final admission, there was a sudden increase in the severity of congestive heart failure, perhaps as a result of stopping digitalis or of recurrence of rheumatic infection. A marked precordial thrust was palpable in the left midaxillary line, suggesting the possibility that such cardiac enlargement might have been on a basis of progressive valvular disease. When such enlargement follows generalized involvement of the myocardium, as in acute rheumatic fever or myocardial infarction, the apical thrust is feeble.

The outstanding feature of the final admission was anuria. At first, congestive heart failure seemed sufficient to account for it, but the urine finally passed was bloody. Was this glomerulonephritis or a toxic nephrosis resulting from the use of a mercurial diuretic? It is generally believed that mercurial diuretics do not ordinarily damage the kidney. This, however, is not an ordinary situation. One of the most important factors in toxicity of these drugs is the rate of renal excretion. That was brought out when the use of xanthine derivatives with mercurials was first introduced. It was seen that the mixture produced much more rapid excretion than the mercurial alone and was less toxic in animals. Here a considerable quantity of Mercupurin was held in the body for a long time, and thus may have affected some kidney damage. Glomerulonephritis or pyelonephritis usually turns up unexpectedly at these conferences, and I think that we have to consider the possibility of both, although at no time in the past had there been any indication of significant renal disease.

Did this man have a generalized disease that involved the kidney, such as periarteritis nodosa? Disseminated lupus erythematosus must also be considered, although the course is too long. I believe that lupus can be discarded almost immediately.

The only diagnosis that might tie the whole thing together, so far as the cardiac picture is concerned, is recurrent active rheumatic fever, with chronic progressive aortic-valve disease — stenosis and regurgitation. Perhaps regurgitation was predominant at first, later becoming secondary to stenosis, at it often does. I should not be too surprised if he had some stenosis of the mitral valve, even though there was no evidence of it in the x-ray films and it was never picked up clinically.

What other etiologic types of heart disease should be considered? Sclerosis of the coronary arteries alone rarely produces congestive failure. Congestive heart failure often follows myocardial infarction, but the electrocardiograms in this case did not suggest infarction at any time. There is a group of destructive myocardial processes falling under the heading of Fiedler's myocarditis. Such patients eventually develop congestive heart failure, but they die after a relatively short time, judging from most of the reported cases of the disease.

DR. GREENE FITZHUGH: Would the fact that no pulsation was detected in the dorsalis pedis arteries indicate a fair amount of vascular disease? Of course, it might have been because the patient was in shock.

DR. WILLIAMS: He was also fibrillating at that time. It is not stated whether the pulsations appeared later.

CLINICAL DIAGNOSIS

Rheumatic and hypertensive heart disease, with congestive failure.

DR. WILLIAMS'S DIAGNOSES

Rheumatic heart disease, with aortic stenosis and possibly regurgitation.
Recurrent rheumatic fever.
Cardiac enlargement.
Congestive heart failure.
Toxic nephrosis (mercury)?
Glomerulonephritis?

ANATOMICAL DIAGNOSES

Acute nephrosis (? Mercupurin).
Acute glomerulonephritis.
Cardiac hypertrophy, rheumatic, coronary and hypertensive types.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed an extremely large heart, weighing about 800 gm. This man did have systolic hypertension all the time, and I am wondering whether that may have played some role in the hypertrophy, because, as was suggested, the valvular disease was not particularly prominent. There was slight thickening of the

mitral valve, and slight interadherence of the aortic cusps. The amount of stenosis in these valves was slight, but they probably did contribute to the heart failure, because we found no other cause for enlargement of the heart.

DR. WILLIAMS: Did you find any evidence of old rheumatic myocarditis or anything of that sort?

DR. CASTLEMAN: No; not in the sections that we have seen.

DR. WILLIAMS: How about the coronary arteries?

DR. CASTLEMAN: They showed severe sclerosis, but we did not find any evidence of old infarction. They were extremely narrow.

The striking finding in the case was in the kidneys. Together they weighed 800 gm., which is almost three times the normal weight. They were markedly swollen, red and mottled, and on section there was no clear line of demarcation between the cortex and the medulla. Microscopically, every glomerular tuft was completely packed with polymorphonuclear leukocytes and almost all the capillary loops were occluded; in other words, they showed the characteristic findings of acute glomerulonephritis. In a few areas we were able to find beginning proliferation of the capillary endothelium of the glomeruli, indicating that the process had been going on for several weeks. I do not know whether or not it antedated that period, but certainly the duration was no longer than a month or six weeks. Most of the convoluted tubules showed epithelial degeneration. This was much more than a mere cloudy swelling; it was a true nephrosis. There were also fat granules within some of the epithelial cells and within the lumen. Several of the tubules already showed evidence of regeneration and repair. We know that repair can occur within three or four days after the onset of necrosis, so that we have evidence here of some injurious agent that had attacked the tubules quite recently. Of course, in this particular case we should like to incriminate Mercupurin, and indeed, I do not see how it can be avoided. When he came to the Emergency Ward five days before admission to the hospital, he complained of edema and said that he had stopped taking digitalis; at that time he was given 1 cc. of Mercupurin. If we assume that he had a glomerulonephritis at that time, it is possible that the Mercupurin was enough to injure the tubules to this extent. He died five or six days later, which would give enough time for the repair process to have begun. I believe that this is the first case that we have ever had in which there has been as much suggestive evidence of injury to the kidneys by Mercupurin.

I looked up the subject two months ago, not extensively, to be sure, and in the only two cases that I could find the patient had also been given bismuth for syphilis, so that no conclusions were possible.

DR. JOSEPH GARDELLA: This man had a severe case of poison-ivy dermatitis and was given subcutaneous injections of material made up by his local doctor. It came in a vial, was mixed in a glass and pounded for a while and was then injected.

DR. CASTLEMAN: Do you mean that this material might have been the toxic agent rather than the Mercupurin?

DR. GARDELLA: He received no diuretic effect from Mercupurin, but it did not seem to make him particularly worse.

DR. FITZHUGH: Did you not say that the glomerular damage was of several weeks' duration?

DR. CASTLEMAN: That was a different process; it was not due to Mercupurin, just a straight glomerulonephritis, which can occur even in a person of eighty. That is the reason why I believe that the Mercupurin might have been an added insult to a previously injured kidney, but as Dr. Gardella has just brought out, it is quite possible that whatever he received for the poison-ivy rash might have been the causative factor.

DR. WILLIAMS: Do you ever see this histologic picture in the course of glomerulonephritis?

DR. CASTLEMAN: Not so severe as this. The kidneys usually do not weigh so much. I was puzzled by this combination of processes and showed the slides to Dr. Frederic Parker, Jr., at the Boston City Hospital, asking him whether it was possible to get this picture in straight glomerulonephritis. He said that he had never seen it. He thought that the reparative changes in the tubules were fairly good proof that there was a toxic agent in addition to the nephritis.

CASE 31452

PRESENTATION OF CASE

An eighty-six-year-old man entered the hospital complaining of a chronic cough.

The cough, which was of a month's duration, was productive of tenacious white sputum and occasionally blood streaked. During this period he had also noticed increasing dyspnea, as well as swelling of the right ankle. He had had occasional chills and fever, the last episode occurring one week before admission. The urine had been yellowish red for several months; he had nocturia. The past history was noncontributory.

Physical examination revealed a well developed and well nourished man in no distress. A diffuse maculopapular eruption was seen over the back, and there were a few excoriated lesions on the dorsum of each hand. The tongue was dry and furrowed. The point of maximum cardiac impulse was in the fifth interspace 10.5 cm. to the left of the midline. A systolic murmur was heard at the apex. Over the right lung base there was flatness, with decreased fremitus and rales. There was bilateral ankle edema, more marked on the right than on the left. The reflexes were physiologic.

The temperature was 99°F., the pulse 110, and the respirations 25. The blood pressure was 160 systolic, 75 diastolic.

Examination of the blood revealed a red-cell count of 3,100,000, with 12.5 gm. of hemoglobin, and a white-cell count of 3900. The urine gave a +++ test for albumin. The sputum was yellowish and negative for acid-fast bacilli. A moderate number of Type 3 pneumococci were found on culture of the sputum. The nonprotein nitrogen was 86 mg. per 100 cc.

An x-ray film of the chest taken the day of admission showed the left lung to be clear. In the right lung there was a hazy, flecky area of increased density in the central portion, with continuous areas of increased density in the lower lung field. There was no evidence of pleural fluid. The heart was prominent in the region of the left ventricle, and the aorta was tortuous. A film taken three days later showed the process to be chiefly in the right middle lobe, with some changes in the lower lobe. The general appearance was that of an extensive peribronchial process involving the middle and lower lobes.

During the patient's hospital course, the temperature varied from 98 to 100°F., rising on one occasion (three days before death) to 104°F. During the first two days his condition was good. On the fifth hospital day, however, his respirations increased to 58 per minute and he had shaking chills. The skin was hot and moist. The lower half of the right lung posteriorly was dull to percussion, with bronchial breathing in this area. Penicillin was begun, 16,000 units being given every two hours. There was no evidence of cardiac failure. The following day the temperature was 98.8°F., and the respirations were slower and less labored. Dullness and bronchial breathing persisted in the lower portion of the right lung. One day later, severe dyspnea again appeared and both lungs were full of coarse bubbling rales. The patient expired on the eighth hospital day.

Differential Diagnosis

Dr. Arthur J. Linenthal: I should like to inquire whether the urinary sediment was examined and whether blood cultures were taken. If so, what did they show?

Dr. Ronald C. Sniffen: The urinary sediment is not reported, and no blood cultures were taken.

Dr. Linenthal: We have an eighty-six-year-old man who came in complaining of cough and blood-streaked sputum for one month, both of which seem to point to some pulmonary process. I think that it is impossible in this case to find one diagnosis that will explain all the abnormalities this man had, and I shall first mention several things that I believe cannot be included in the primary diagnosis.

It is interesting that this man was apparently in good general condition. He was well developed and well nourished, and during the first two or three hospital days his condition was thought to be good. This must have been true, because apparently no specific therapy was started. He had some skin lesions on his back, which were possibly associated with uremia, a condition that sometimes produces skin lesions. They might have been related to drugs taken before admission, or they might have been due to pressure, since I assume that this patient was probably in bed for a short time before he came to the hospital. The excoriated lesions on the hand are not significant; they were probably senile keratoses.

The patient had hypertension on admission, and the blood pressure might well have been higher previously. Probably associated with hypertension, he had cardiac enlargement, demonstrable both by physical and by x-ray examination. He had a systolic murmur at the apex that could well have been the systolic murmur of functional mitral regurgitation associated with left ventricular enlargement, as part of what we might call the cardiac picture. He had bilateral ankle edema; we are not told whether it was pitting. The serum protein level is not given. A low serum albumin might have been of interest in a patient with albuminuria. The dyspnea might also have been related to the cardiac enlargement, although of course it could have been due to the pulmonary factor. It seems as though he might well have had a mild degree of congestive heart failure.

He also had a +++ albuminuria, an elevated nonprotein nitrogen and slight anemia, which point toward some renal lesion, and in a patient of this age it seems likeliest that he had a chronic arteriolar nephrosclerosis. The description of the yellowish red urine for several months before he came to the hospital is interesting but impossible to evaluate. He had had some nocturia, which is not too surprising in a patient of this age, and it could have been related to the mild cardiac failure, to renal failure or to benign prostatic hypertrophy.

We then come to the pulmonary picture, which was the presenting problem, the cough, sputum, hemoptysis and dyspnea all pointing to a lesion of the lungs. Physical examination showed some abnormality, and x-ray examination revealed a rather extensive process.

May we see the x-ray films?

Dr. Clayton H. Hale: These films show the uniform process described. We see the linear markings, described as peribronchial extension, throughout the greater portion of the right lung field. There is some increased density in the lower lobe. The shadow of the diaphragm is fairly well obscured posteriorly. I think that one also has to say that there is definite abnormality in the upper lobe. There is no significant amount of fluid in the chest. If this is pulmonary edema, it is not on a cardiac basis, since I cannot make out any enlargement of

the vascular shadow on the left. We must also consider metastatic malignancy in the right lung, possibly with superimposed pulmonary edema. The findings could also be due to diffuse areas of consolidation on an infectious basis.

DR. JOSEPH AUB: Is there any collapse of the right lower lobe?

DR. HALE: I do not believe so, although it may be a little smaller than normal. At least it is not aerated, which suggests fluid or consolidation.

DR. LINENTHAL: In discussing the pulmonary process there are several types of conditions that one must consider — infection, carcinoma and, as Dr. Hale suggests, pulmonary edema, or possibly a combination of two of these three possibilities. It is important to know that apparently there was no past history of pulmonary symptoms.

So far as infection is concerned, the bouts of fever and chills that this man had are consistent with an infectious process, due either to a primary infection or to a neoplasm with secondary areas of necrosis or infection. We are given a clue in the laboratory examinations to one specific bacterial agent, namely, a Type 3 pneumococcus, which grew in moderate amounts in a culture of the sputum. The picture certainly was not that which we are accustomed to see in the majority of people with pneumococcal pneumonia: there was no acute onset; the patient was not acutely ill and had no chest pain; and he had no fever except during the episode of chills. Furthermore, the duration was rather long for a pneumococcal pneumonia. In an eighty-six-year-old man, however, pneumococcal infection can behave peculiarly, and one may find a pathologic process that is entirely out of proportion to the general condition of the patient; in other words, the general condition of the patient may continue to be quite good in spite of the fact that the pathologic process is extensive. The normal white-cell count is interesting, and I suppose that it represents the inability of this old man to respond to an infection in the lungs, just as does the absence of any striking continued fever. The Type 3 pneumococcus is a rather frequent organism in the normal upper respiratory tract, and this fact makes the situation a bit confusing. It is also, however, one of the types of pneumococci usually found in older people, and probably because of this the pneumonia that it produces has a higher mortality rate than those caused by other types.

Another possibility that one thinks of in passing is tuberculosis. It seems unlikely on the basis of the patient's age and on the basis of the x-ray picture, and at least one examination of the sputum was negative for acid-fast organisms.

The question of atypical or so-called "virus" pneumonia should be mentioned, but there seems to be little in the picture to make one think too strongly of that. One might also think of a chronic or perhaps subacute nonspecific bacterial inflammatory process in the lung, so-called "chronic pneumonitis." There is no history of a pre-existing underlying pulmonary lesion on which this might have been superimposed, but the patient was an old man and he had uremia, both of which might have increased his susceptibility to infection. The chills and fever would also be consistent with chronic pneumonitis.

Did this man have a carcinoma of the lung? As Dr. Hale mentioned, the x-ray picture may be that of metastatic disease. There is nothing to indicate a primary tumor elsewhere. The urinary tract is suspect, but I think that the findings can be explained on the basis of hypertensive disease. The development of symptoms, beginning with cough and blood-streaking rather than with gross hemoptysis, and the chills and fever are consistent with pulmonary carcinoma. The duration is rather short but is possibly accounted for by a superimposed infection on a carcinoma that had been silent for a time previous to the onset of symptoms. The x-ray lesion is rather extensive for a primary neoplasm of the lung, involving as it probably does all three lobes, with the major process in the right middle lobe. Certainly if he did have carcinoma, he must have had a rather extensive superimposed infection.

In the hospital he had an episode of rapid respiration and dyspnea, which was probably associated with the chills and fever, and it seems that this was similar to the previous episodes of chills and fever. The next day, the temperature came down to normal and he was apparently much better. The record states that he had no evidence of cardiac failure at that time. I assume that this probably means that the lungs were not full of bubbling rales. Penicillin was begun at that time. The patient was better the next day, but I see no reason to believe that the improvement was due to the penicillin.

The terminal episode, which followed two days later, was apparently one of acute pulmonary edema. This could well have represented an extension of the pulmonary infection, or it might even have been associated with a massive myocardial or pulmonary infarction.

In summary, I think that this man had a subacute pulmonary infection, probably due to a Type 3 pneumococcus. I believe that a neoplasm of the lung is unlikely. In addition, I believe that he had hypertensive cardiovascular disease and marked nephrosclerosis, which caused nitrogen retention and cardiac enlargement.

DR. AUB: Would Dr. Linenthal consider a primary tumor of the kidney — a hypernephroma or renal-cell tumor?

DR. LINENTHAL: It is possible. On the basis of the evidence we have, I do not see how one could go any farther than to raise the question.

DR. J. H. MEANS: I saw this man and wrote the following note: "The patient is an eighty-six-year-old man and rapidly recovering from whatever

ailed him. It is good geriatrics to get him up as soon as possible and let him do about as he pleases." Shortly after that the service changed, and apparently he stayed in bed and died. I wonder if they had gotten him up whether he would still be with us.

DR. W. WILSON SCHIER: The terminal episode suggests pulmonary embolism — the high respiratory rate, the fever and the low white-cell count.

DR. LINENTHAL: I mentioned the possibility of pulmonary infarction to explain the terminal episode. It could also have been due to a massive pulmonary embolism without infarction.

DR. WADE VOLWILER: I remember this man because his case taught a valuable lesson to the house staff. In the first place, because of the emphasis that he continually placed on the blood-streaking of the sputum, which occurred daily and began with the onset of the productive cough, we thought that he must have a neoplasm of the lung as the basis of his difficulties. We also believed that he had a certain amount of secondary infection behind the process.

The cough was extremely productive.

He was a well preserved, agile man of eighty-six and was kept out of bed as much as possible, even after Dr. Means left the service. The immediate problem arose whether we should investigate the process further by means of bronchoscopy and other such procedures. Because of his age, a severe cervical hypertrophic arthritis and our inability to do much about an extensive carcinoma if we did find it, we elected not to do a bronchoscopy. We did decide, however, to give him one course of penicillin therapy to relieve any secondary infection that might have been present, but this was not done until the morning of the day on which he had the shaking chill and rapid respirations. He then went downhill rapidly and died in coma.

I believe that the elevated nonprotein nitrogen was found in a blood specimen taken in the terminal days, at which time he was quite dehydrated. At no time did we believe that he had signs of cardiac failure: there was little cyanosis, the neck veins were not distended and did not pulsate, there was no gallop rhythm, and the pulse generally was regular.

CLINICAL DIAGNOSIS

Pneumonia?
Carcinoma of right lung?

DR. LINENTHAL'S DIAGNOSES

Subacute pulmonary infection (Type 3 pneumococcus).
Hypertensive cardiovascular disease.
Nephrosclerosis.

ANATOMICAL DIAGNOSES

Bronchopneumonia, bilateral.
Chronic bronchitis.
Pleuritis, acute fibrinous, left.
Nephrosclerosis, slight.
Cerebral infarcts, old.

PATHOLOGICAL DISCUSSION

DR. SNIFFEN: The important findings at autopsy were confined to the chest. The right pleural cavity merely showed fibrous apical adhesions. The left cavity was entirely obliterated by old fibrous adhesions and more recent fibrinous adhesions. The lungs were three to four times their normal weight — 2250 gm. Throughout the entire left lung and in the right upper and lower lobes there were large patchy areas of gray consolidation; the right middle lobe was edematous. The heart weighed 440 gm., a little above the upper limit of normal, but was essentially negative, apart from a mild coronary atherosclerosis. A blood culture was sterile.

Microscopically, sections of the lungs showed an extensive and severe bronchopneumonia, and judging from the condition and quality of the exudate, it seemed to be of approximately one week's duration. The bronchi, on the other hand, showed chronic changes, in that there were fibroblastic proliferation in the walls, slight epithelial metaplasia and a few partially organized fibrinous plugs in the lumens. The kidneys showed a mild nephrosclerosis and a suggestion of pyelonephritis.

DR. MEANS: What was the state of the aorta?

DR. SNIFFEN: Remarkably free of atheromatous change.

DR. MEANS: Dr. Albright is always quoting the late Dr. Erdheim as saying that if one lives to be over eighty, one must have a smooth aorta, because if one does not have a smooth aorta, one does not live to be over eighty. We do not get autopsies often on octogenarians. It might be worth while to call your attention to an interesting clinicopathologic conference by Dr. Holyoke, of Salem. He lived to be over one hundred years old and made an anatomical diagnosis on himself. He requested that all the doctors in Salem be invited to see his autopsy. Most of them came. It was stated that the aorta was just as smooth as a youth's and that the heart was absolutely normal, indeed on the small side. An autopsy on anyone over eighty is of interest from that angle. The present one seems to bear out Dr. Erdheim's statement, although I recall one patient over eighty who had a rough aorta; so the maxim does not always hold.

DR. CHARLES S. KUBIK: The pathology in the brain contributed nothing to the symptomatology described here. There were a number of small infarcts, the larger ones being in apparently silent areas in the frontal and occipital regions.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

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Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year (Boston funds); $8.52 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, two weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts.

FIFTIETH ANNIVERSARY OF THE DISCOVERY OF X-RAYS

Just fifty years ago today, November 8, 1895, a new epoch in medicine was opened with the discovery of the x-ray by Wilhelm Conrad Roentgen. Although the ray has been officially designated the "roentgen ray" in his honor, the more convenient name Roentgen first employed, "x-ray," is generally used. Roentgen not only discovered the x-ray and described its properties, but he also observed that this ray would penetrate certain opaque objects, among them the human body. The medical world was quick to perceive the great diagnostic and therapeutic possibilities of this ray. Nearly all the organs of the body are now accessible for study either directly or indirectly. Carefully controlled voltages from 20,000 to 3,000,000 are available for therapeutic work alone or in conjunction with radium. Lately, the armamentarium has been increased by artificially produced radioactive substances, some for internal use, the application of which is being explored.

The first chapter of the x-ray era was written by keen clinicians employing this new modality as an aid toward better diagnosis. These pioneers made good use of their knowledge of anatomy, physiology and pathology to discover methods of examination and treatment. Progress since then has been a race between the development of more powerful and more versatile apparatus and its adaptation to the fields of diagnosis and treatment.

Lest the young enthusiast be inclined to rest on his laurels, a review of the first decade of x-ray progress will bring with it a humble frame of mind. It is amazing that the early investigator who unknowingly risked his life with the crudest of makeshift equipment produced so much. Between the years 1895 and 1901, Francis H. Williams, William Rollins and Walter B. Cannon, to mention just a few, outlined many of the fundamental diagnostic and therapeutic criteria used today. It was Williams who threw a bombshell into a meeting of a medical society by maintaining that he could discover pulmonary tuberculosis by this new method earlier than by auscultation and percussion. In 1901 Williams's reports of cases treated by x-ray would put many modern physicians to shame because of their completeness — a good history and description of the lesion, a biopsy done by Frank B. Mallory, detailed data of the technic used, extensive progress notes and photographs taken before and after treatment to document his results.

The importance of the fluoroscopic examination was emphasized by Williams, Crane, Rieder, Carmen and others from the inception of the specialty. It was one of the earliest tools, and only through the fluoroscope can the living dynamic aspects of anatomy, physiology and pathology be studied. Roentgenoscopy and roentgenography should be considered and used as complementary procedures for

thoracic, gastrointestinal, spinographic and foreign-body examinations. The fact that it is time consuming and requires special skill should be no excuse for failure to use fluoroscopy in modern radiologic practice.

Those who were responsible for these early advances had an excellent clinical background, a sound knowledge of the basic sciences and an investigative mind. Little insight is needed to recognize that this is as true now as it was then.

The second chapter of this era was one of consolidation and comprised establishing standards for good radiologic practice and making them possible by a well planned training program. The medical profession had recognized radiology as a full-fledged specialty. In 1924 the American College of Radiology was founded for the purpose of studying and correlating the educational and economic aspects of radiology, to advance this science and to improve its services. In 1934, the three American radiologic societies, the College of Radiology and the Section on Radiology of the American Medical Association recognized the necessity for establishing high minimum requirements for physicians practicing this specialty. They founded the American Board of Radiology, with an examining panel to certify diplomates in five categories according to the training and experience of the applicant: radiology (the practice of the entire specialty); roentgenology (excluding the practice of radium therapy); diagnostic roentgenography (excluding all therapy); therapeutic roentgenology (excluding diagnostic practice); and radium therapy. The applicant must hold himself out to be a specialist in radiology or one of its branches and must have the following minimum training requirements: a graduate of a Class-A medical school; a one-year internship in an approved hospital; and a three-year residency in radiology, including six months of applied pathology and a grounding in the basic sciences and the theories of radiation. In addition, an examination by the Board must be passed for certification. Statistics show that one out of every three applicants fails.

As a corollary to the above requirements, a training program for radiologists had to be initiated. The American Board of Radiology, in co-operation with the Council on Medical Education and Hospitals of the American Medical Association, has helped establish standardized residencies in American teaching hospitals to satisfy the demand for well trained radiologists. There are over one hundred such residencies available at present, and every effort is being made to increase this number so that any qualified returned medical officer who desires to follow the specialty can be trained.

The next chapter lies in the future. Adequate tools and technics are available. The specialty has established high standards and an educational program to meet them. In the next few years enough well trained radiologists will be on hand to offer modern radiologic services to both large and small hospitals and to private practice as well. The future of radiology is closely integrated with the future of medicine as a whole. Progress depends more than ever on the true co-operative spirit among the various branches of medicine, pooling individual skills and knowledge. It is no longer good medicine to be a "lone wolf" in handling problem cases.

The duty of the radiologist is not to confirm the clinical impression but to give a radiologic consultation, which, when added to the clinical and laboratory data, will lead to a correct diagnosis. Therefore, he must have at hand pertinent data concerning the patient at the time of the examination. It is hoped that the return of doctors from the armed services will allow the physician of tomorrow enough leisure to make use of the opportunity for consultation and discussion, which were not possible in the rushed wartime years. It is through the medium of this exchange of ideas that medicine will advance with the same strides that it has in the past.

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MISCELLANY

FEDERAL PUBLIC-HEALTH ADMINISTRATION

The Association of State and Territorial Health Officers has recently expressed cognizance of the need of co-ordination, under a single head, of the civilian health activities of the federal government. The several states and territories have been receiving grants-in-aid from both the United States Public Health Service and the Children's Bureau of the Department of Labor for their public-health programs. Originally these grants were made under the Social Security Act, but more recently the grants from the United States Public Health Service have been made under the recodification of the laws pertaining to the public health, known as Public Law 410 of the Seventy-Eighth Congress.

At the present time the several states are required to make reports to both agencies, present their budgets and conform with a variety of regulations issued by these two agencies. In an endeavor to reduce the number of different reports required and to co-ordinate the directives coming from the various federal health agencies, it is the recommendation of the Association that, in the reorganization of the Government, as is being planned by President Truman, serious consideration be given to the establishment of a department of public health with a cabinet officer in charge. It is further recommended that permanent career men be selected for the key positions in this department and that they be given an opportunity to retain their positions on a permanent basis.

The Association has learned that a proposal may have been made for the organization of a department of public health and welfare with a cabinet officer at its head. If this organization is carried through, the Association suggests that adequate measures be taken to ensure that public health receives sufficient freedom of action to carry on its important function of maintaining optimal health for all the people. It is further suggested that, if such a combined department is formed, permanent career undersecretaries or assistant secretaries should be in charge of the two activities and that they should be of equal rank. The Association believes that such a department would be less desirable than a separate department of public health.

These recommendations were made, the Association states, in the interest of better public-health administration on a federal level and of the co-ordination of all civilian public-health activities in a single department, thereby rendering liaison and co-operation with the several states and territories the more efficient and effective. This, in turn, would bring about an improvement in general public-health work throughout the entire country and enable such a department to administer any future legislation pertaining to public health with greater efficacy and with a smaller administrative overhead for services rendered.

NOTICES

ANNOUNCEMENT

Dr. A. Louis Hermanson has resumed the practice of surgery at 371 Commonwealth Avenue, Boston.

Dr. Antonio P. Milone, who has been discharged from the armed services, will resume practice at 4354 Washington Street, Roslindale, on November 15.

Dr. Arnold L. Segel announces the opening of his office at 475 Commonwealth Avenue, Boston, for the practice of general surgery.

SUFFOLK DISTRICT MEDICAL SOCIETY

The fall dinner of the Suffolk District Medical Society will be held at the Harvard Club of Boston on Saturday, November 17. Guests will assemble at 6:00 p.m., and dinner will be served promptly at 7:00 p.m. The speaker will be Brigadier General Elliott C. Cutler, M.C., A.U.S., whose subject will be "Experiences in the European Theater of Operations."

This is to be a "home-coming meeting," and all members of the district society are urged to bring as their guests men who have been recently discharged from service or those who are still in uniform; the latter will be admitted without charge, regardless of whether or not they are members of the Massachusetts Medical Society. In addition, the members of other district societies are urged to attend. Tickets may be purchased from the treasurer, Dr. Richard S. Eustis, 319 Longwood Avenue, Boston 15. Contrary to the custom adopted for the past several years, wives of members will not be admitted.

EXHIBITION AT BOSTON MEDICAL LIBRARY

In commemoration of the fiftieth anniversary of the discovery of the x-rays by Konrad Roentgen, the Boston Medical Library has displayed in the showcases in the rotunda the original papers of Roentgen, together with other material on the history of radiology.

AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

The sixty-ninth annual meeting of the American Association on Mental Deficiency will be held at the Hotel Cleveland, Cleveland, on November 28, 29 and 30 and December 1. The program, as arranged, presents sections on institutional administration, research, psychiatry and medicine in the field of mental defect, psychology and teacher training.

NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Harvard Club of Boston on Friday, November 16, at 8:00 p.m. The fiftieth anniversary of the discovery of x-rays will be commemorated by a special program consisting of the following:

The Use of X-rays in Art. Dr. William J. Elliott.
Some Industrial Applications of X-rays. Dr. Paul E. Tivnan.
The Application of X-rays to Crime Detection. Dr. Joseph T. Walker.
X-rays as a Tool of the Physicist. Dr. Bertram E. Warren.
X-rays in Medicine. Dr. Merrill C. Sosman.

Interested physicians are invited to attend.

SUFFOLK CENSORS' MEETING

The Censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, on Thursday, December 6, 1945, at 4:00 p.m.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, November 20, at 8:15 p.m. Drs. Chester S. Keefer, Max Finland and Charles A. Janeway will present a symposium on recent advances in chemotherapy.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, November 15

Friday, November 16

*9:00–10:00 a.m. Deep Phlebitis and Pulmonary Embolus. Dr. Jacob A. Fine. Joseph H. Pratt Diagnostic Hospital.

*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Acrodermatosis Related to Vascular Diseases. Dr. Eugene E. O'Neil. (Postgraduate clinic in dermatology and syphilology.) Amphitheater, Dowling Building. Boston City Hospital.

*8:00 p.m. New England Roentgen Ray Society. Harvard Club of Boston.

Saturday, November 17

*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

(*Notices continued on page xvii*)

NOTICES *(Continued from page 576)*

MONDAY, NOVEMBER 19
*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, NOVEMBER 20
*9:00–10:00 a.m. Medical clinic. Infants' Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.
8:15 p.m. Greater Boston Medical Society. Beth Israel Hospital.

WEDNESDAY, NOVEMBER 21
*9:00–10:00 a.m. Evolution of Industrial Medicine. Dr. Dwight O'Hara. Joseph H. Pratt Diagnostic Hospital.
*12:00 m. Clinicopathological conference. Children's Hospital.
*12:00 m.–1:00 p.m. Clinicopathological conference. Cambridge Hospital.

*Open to the medical profession.

OCTOBER 1–DECEMBER 10, 1945 and JANUARY 7–APRIL 22, 1946. Metropolitan State Hospital. Eleventh postgraduate seminar in neurology and psychiatry. Page 314, issue of September 6.
NOVEMBER 2, 9 and 16. Salmon Lectures. Page 514, issue of October 25.
NOVEMBER 13. Harvard Medical Society. Page 546, issue of November 1.
NOVEMBER 15. New England Pathological Society. Page 546, issue of November 1.
NOVEMBER 16. New England Roentgen Ray Society. Page 576.
NOVEMBER 17. Suffolk District Medical Society. Page 576.
NOVEMBER 20. Greater Boston Medical Society. Page 576.
NOVEMBER 28–30 and DECEMBER 1. American Association on Mental Deficiency. Page 576.
DECEMBER 13. The Treatment of Venous Thrombosis. Dr. Robert R. Linton. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
FEBRUARY 2. American Board of Obstetrics and Gynecology. Page 514, issue of October 25.

DISTRICT MEDICAL SOCIETIES

SUFFOLK
NOVEMBER 17. Harvard Club of Boston.
DECEMBER 6. Censors' meeting.

WORCESTER
NOVEMBER 14. Grafton State Hospital.
DECEMBER 12. Worcester City Hospital.
JANUARY 9. St. Vincent Hospital.
FEBRUARY 13. Worcester State Hospital.
MARCH 13. Worcester Memorial Hospital.
APRIL 10. Hahnemann Hospital.
MAY 8. Annual meeting.

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